The Open Nutraceuticals Journal, **2013**, *6,* **(Suppl 1: M7) 89-104**

Chronobiology and Chronomics Honor Douglas Wilson. Neither Calories Nor Anything Else are Equal at Breakfast and Dinner or Along Other Time Scales

Germaine Cornelissen[1,*], R.B. Singh[2], Othild Schwartzkopff[1] and Franz Halberg[1]

[1]*Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA*

[2]*Halberg Hospital and Research Institute, Centre of Nutrition and Heart Research, Moradabad, U.P., India*

Abstract: To honor Douglas Wilson, this paper reviews evidence for studying and quantifying rhythms as the indispensable control, whether to assess the effect of a fixed-calorie meal taken as breakfast or dinner, or to understand how human physiology and pathology may be affected by space-terrestrial weather. Since D. Wilson's work has dealt intensively with salivary hormonal determinations, we illustrate what can be learned from longitudinal series obtained in health or from a patient suffering from adynamic depression episodes recurring twice a year and lasting 2-3 months. The socially less unacceptable collection of serial salivary samples should be introduced more broadly into laboratory medicine for a more refined diagnosis and as a means to guide the optimization of any needed treatment by timing.

Key words: Chronobiology, chronomics, circadian stage-dependent response, isocaloric meal, relative weight loss, salivary hormonal determinations.

HOMMAGE

In the English-speaking realm, one still reads that the same calorie is utilized no differently at breakfast than at dinner, although on the same 2000 calories, three students in a clinical research center all happened to gain weight when they ate a single daily meal 12 hours after awakening on dinner-only for one week and all lost weight when they ate the isocaloric meal within 1 hour after awakening (breakfast-only) for another week, Figs. (**1A**-**1G**) [1-4]. A relative body weight gain on dinner-only (vs. breakfast-only) was also found in the vast majority, and overall on a free-choice meal eaten as dinner-only vs. breakfast-only, Figs (**1A**-**1G**) [1-4]. Chronobiology, the study of biological time structures (chronomes), circadian and other, including cycles covering decades, is thus of interest to nutritionists.

Chronobiology tried to examine time structures with controls in the laboratory and with the standardization of the routine of living in the clinic. Control of manipulable factors involved environmental temperature, humidity, light and darkness, and of course the diet that became the dominant synchronizer of circadians when it was restricted to 50% of the usually consumed calories [3, 5, 6]. Eventually, chronobiologists realized that their time structures, many new ones other than circadian, had counterparts, coperiodisms in space weather that (as yet) cannot be readily manipulated. Weather beyond the atmosphere, however, is sufficiently variable in its time structures to allow the study of biospheric consequences of changes in solar, interplanetary and terrestrial variables, photic and nonphotic, the latter including magnetism and gravity. Chronomics [6] thus came about, and Douglas Wilson, the clinical statistician par excellence, realized its importance and became its advocate, as he was for chronobiology. Both chronomics and chronobiology are inferential statistical endeavors, although many of their practitioners are in the position of Molière's M. Jourdain: "Par ma foi! il y a plus de quarante ans que je dis de la prose *[chronobiology]* sans que j'en susse rien, et je vous suis le plus obligé du monde de m'avoir appris cela" (My goodness, for over 40 years I've spoken prose *[I dealt with chronobiology]* without realizing it! I'm most grateful to you … for telling me) *(Le bourgeois gentilhomme,* Act II, Scene V).

PREAMBLE

This issue honors Douglas W. WILSON's achievements, which follow as his autobiography and bibliography. Two of us have been associated with him in many ways over decades. We met Doug as a cooperating scientist in a study of a bra that by recording temperature over the breast [7-9; cf. 10] aimed to detect changes associated with malignant tumors, as alterations of spectral components. A case study by Michel Gautherie had recorded surface temperature alterations in a cancerous breast monitored concurrently with a presumably healthy contralateral breast over a span sufficient to yield the spectrum of Fig. (**2**) [11, 12; cf. 8]. This

*Address correspondence to this author at the Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA;
Tel: 612-624-6976; Fax: 612-624-9989; E-mail: corne001@umn.edu

1876-3960/13

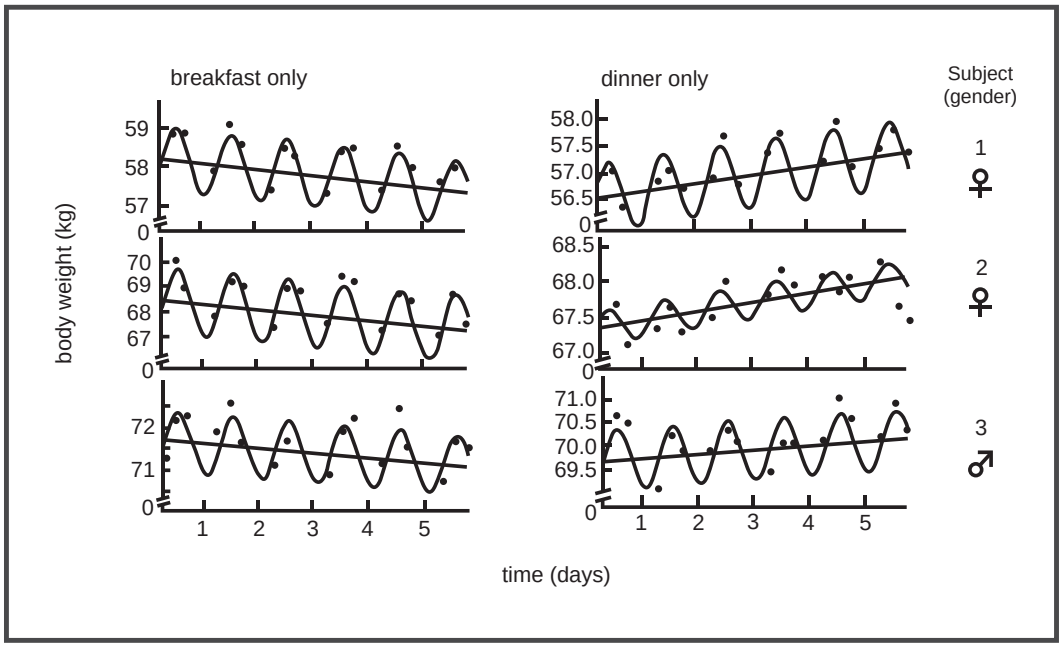


Fig. (1A). Body weight loss on breakfast-only vs. body weight gain on dinner-only in 3 young clinically healthy subjects consuming a single daily meal of 2000 calories. In this limited study, a 24-hour cosine function and a linear trend fitted concomitantly to the data were statistically significant 5 times out of 6 (P<0.05; for non-zero-slope 4 times out of 5). Results confirmed by extensive follow-up studies on ad libitum breakfast-only vs. dinner-only for 3 weeks. © Halberg.

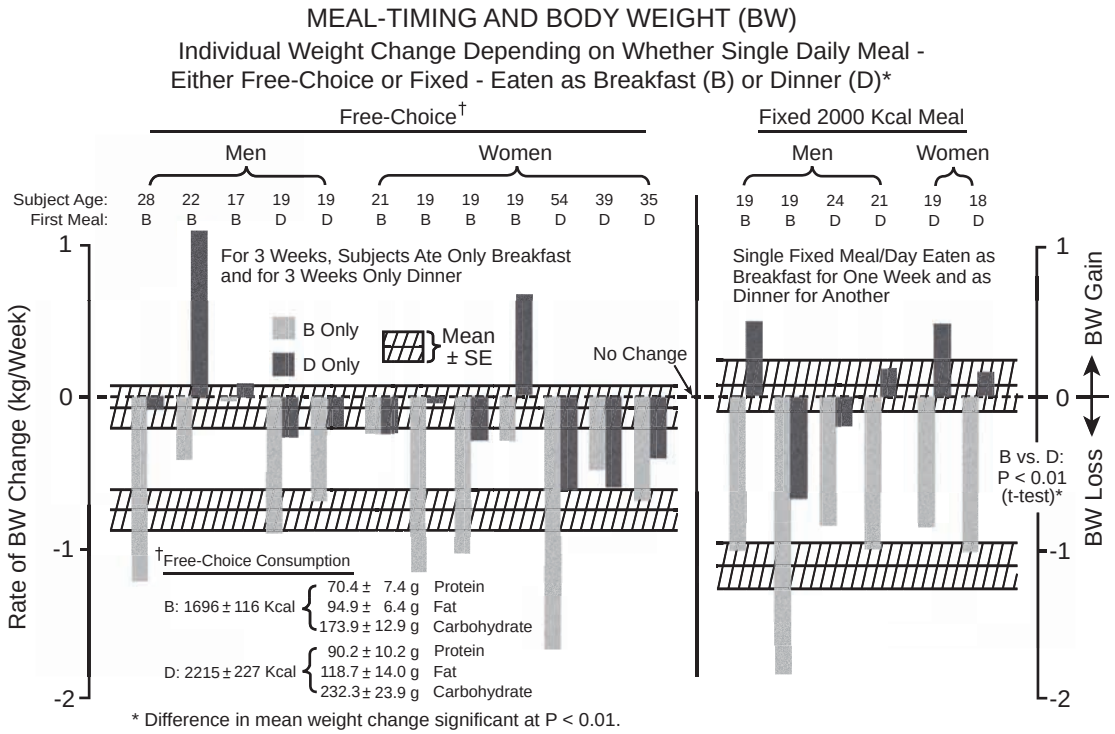


Fig. (1B). In two separate studies of the effect of meal timing on body weight, 9 men and 9 women consumed either a fixed 2,000-calorie meal or a single free-choice meal as breakfast (**B**) or dinner (**D**) (for 1 week on a fixed-calorie meal or 3 weeks on a free-choice meal). Body weight remained more or less unchanged on dinner-only. A decrease of about 1 kg/week was noted on breakfast-only. The rate of body weight change also differed significantly between the two schedules (P<0.02). © Halberg.

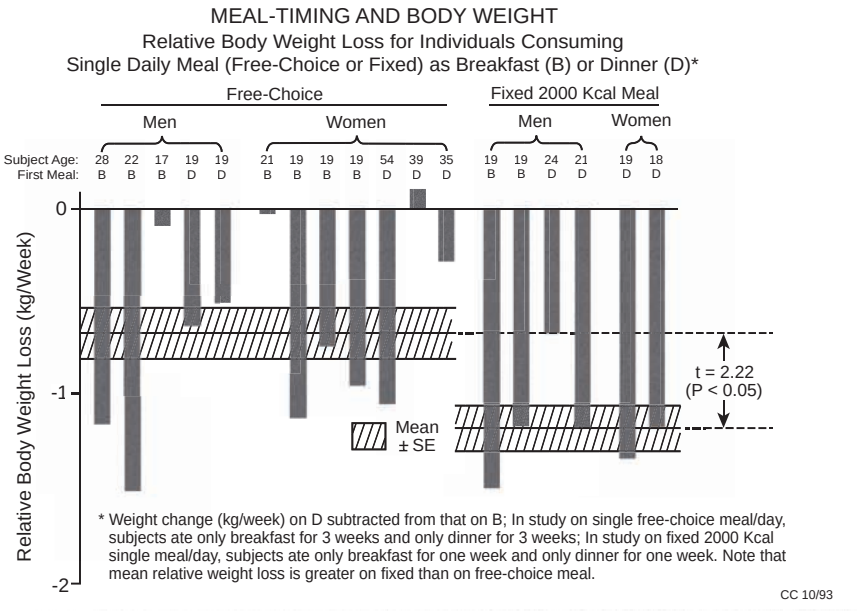


Fig. (1C). Relative body weight loss on breakfast only vs. dinner only for each subject participating in the two studies described in Fig. (**1B**). Only one volunteer gained weight on breakfast vs. dinner. Overall, the difference in relative body weight loss on breakfast (**B**) vs. dinner (**D**) is statistically significant (P<0.05), whether a fixed 2,000-calorie meal (right) or a single free-choice meal (left) is consumed. Weight change (kg/week) on D subtracted from that on B. In the study on one free-choice meal per day, subjects ate only breakfast for 3 weeks and only dinner for 3 weeks. In the study on one fixed 2,000-calorie meal per day, subjects ate only breakfast for 1 week and only dinner for another 1 week. Note that mean relative weight loss is greater on fixed than on free-choice meal. © Halberg.

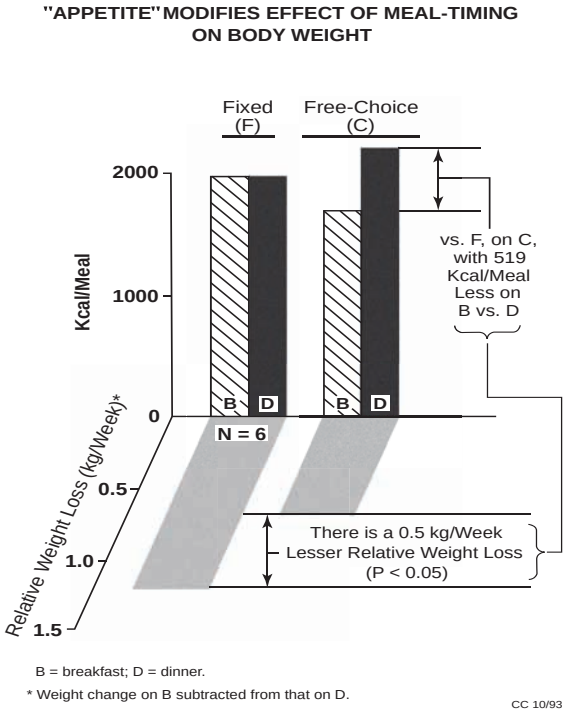


Fig. (1D). Appetite (here defined as choice and amount of food) modifies the effect of meal timing on body weight. Relative body weight loss on breakfast-only (**B**) as compared to dinner-only (**D**) is less when meal is free-choice rather than fixed. An overall summary of relative body weight loss on breakfast-only vs. dinner-only in the two studies indicates that the decrease in relative body weight was more pronounced when a fixed 2,000-calorie meal was imposed than when volunteers could choose what they ate. © Halberg.

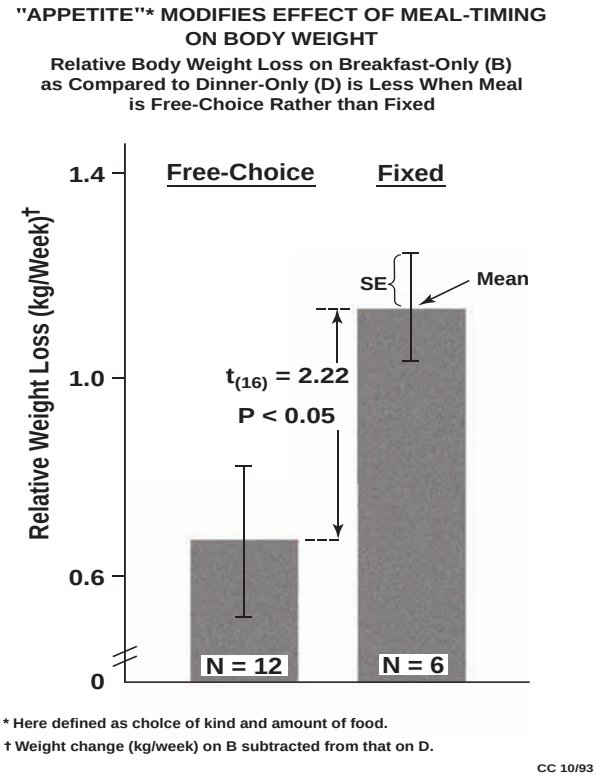


Fig. (1E). Appetite (here defined as choice and amount of food) modifies the effect of meal timing on body weight. The lesser body weight loss on breakfast (**B**) vs. dinner (**D**) observed on a free-choice vs. a fixed 2,000-calorie meal occurred while calorie consumption on the free-choice meal was less (not more) than 2,000 calories per meal. © Halberg.

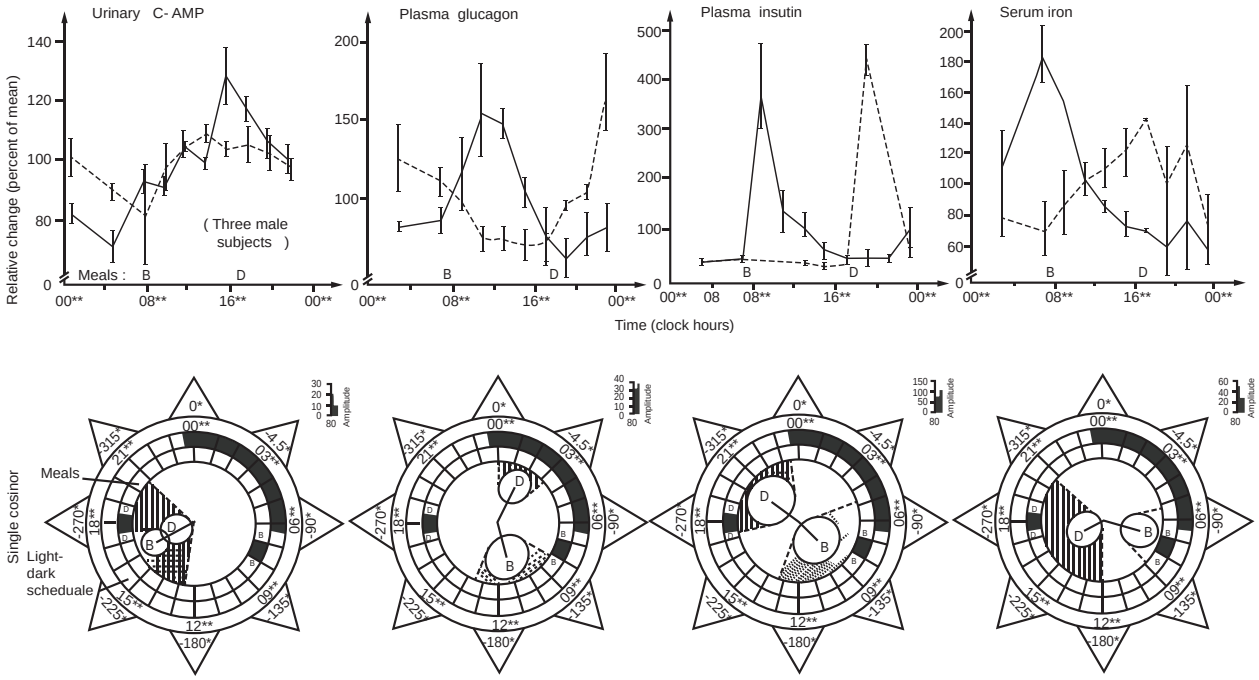


Fig. (1F). Consuming a single daily meal as breakfast-only vs. dinner-only affects the timing of the circadian chronome component differently for different physiological variables in humans. The single daily meal was 2,000 calories given for 7-day spans. Breakfast (**B**), solid line. Dinner (**D**), broken line. © Halberg.

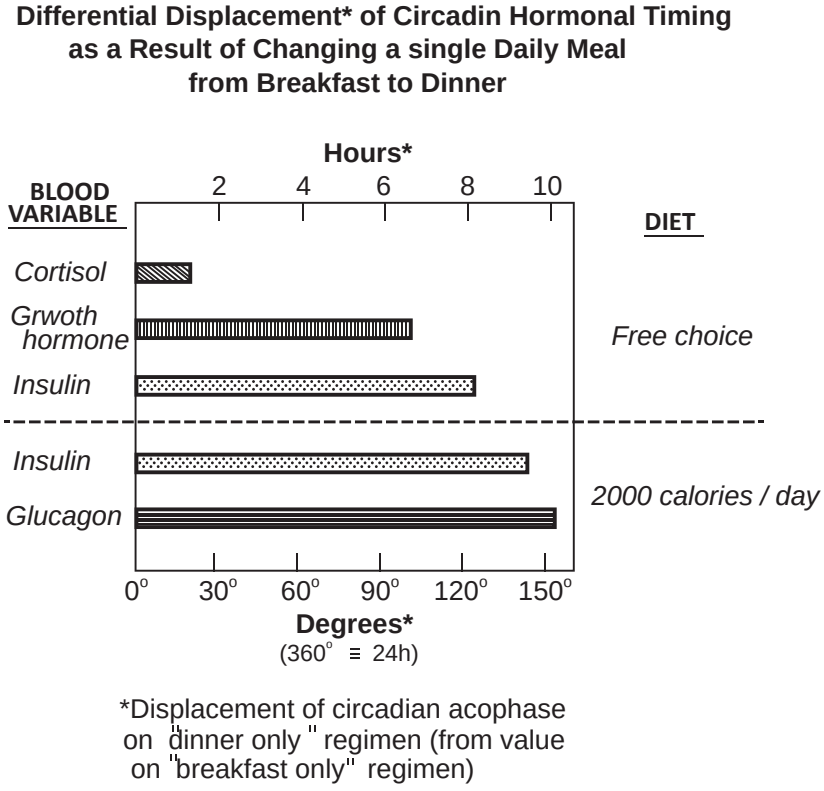


Fig. (1G). Differential displacement of circadian hormonal timing as a result of changing a single daily meal from breakfast to dinner. Whereas the circadian rhythm of circulating cortisol is only slightly affected by the timing of a single daily meal, considerable phase-shifts are observed for the case of growth hormone, insulin, and glucagon, resulting in a different internal timing of the latter three hormones vs. cortisol. © Halberg.

figure reveals a broader than circadian perspective of an organism's time structure, our concern herein. It shows that the precise period of a desynchronized circadian cycle over the cancerous breast may be the result of an infradian frequency demultiplication (rather than a free-run), suggesting the need for a concomitant extra-circadian and circadian assessment in this case or many others, a point made by one of us in invited addresses at the annual meetings of the Royal Statistical Society and the American Statistical Association [13]. Thanks to Doug, one of us also had an opportunity to give a perspective of multifrequency intermodulating rhythms in us, among other instances, at the International Society of Clinical Biostatistics in Copenhagen [14, cf. 15], over which Doug then presided, while two of us later contributed to another meeting also organized by Doug held in Cardiff, Wales [16, 17]. These were welcome opportunities for all authors, who invariably seek to assess in inferential statistical terms, also in the individual patient's time series, the uncertainties in whatever they do or recommend; all in time willingly or unwillingly involve a broad transdisciplinary temporal spectrum, including the products of the human mind, i.e., the chronousphere [6].

Doug was also an officer of the International Society for Research on Civilization Diseases and the Environment (SIRMCE), of which one author was chief US officer and another was US secretary. Our endeavors in that society aimed at prehypertension as a main focus of health care more broadly shifted to non-communicable diseases [18-20]. Our former official cooperation in SIRMCE led to the project on The BIOsphere and the COSmos, BIOCOS, coordinated by one of us (GC). Doug remains an advocate of the chronobiologic approach, developed into chronomics, for broader disease and cataclysm prevention, by monitoring our physiology during wellness, rather than flying blind to any effects of diet, exercise or other intervention, recommended, sometimes implemented but hardly ever surveyed for its consequences during wellness [21]. Exercise at the wrong time can induce an asymptomatic vascular variability disorder, VVD [22].

Douglas Wilson's name is most inextricably associated with salivary studies [23-42], the vehicle to investigate a spectrum of extracircadian components as well as circadian rhythms (with periods between 20 and 28 hours), which are most pertinent to any journal dealing with nutrition. The

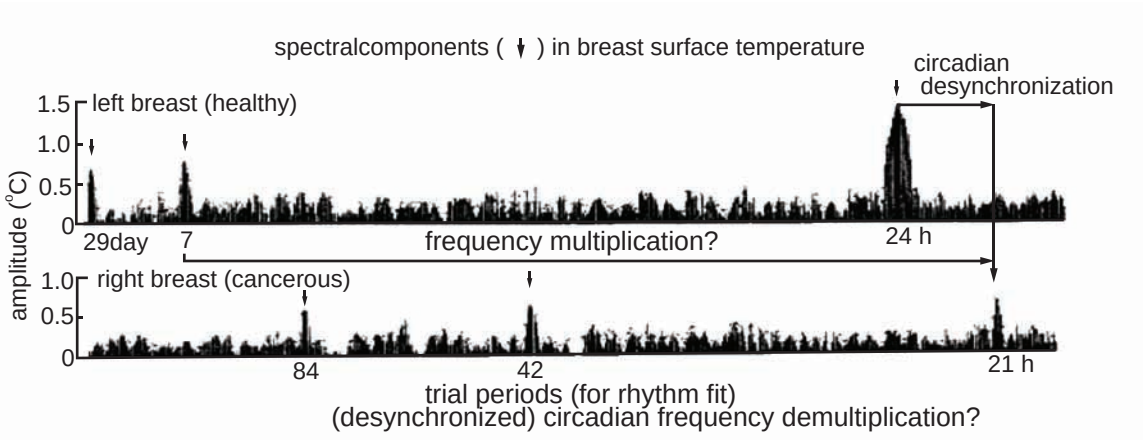


Fig. (2). Analysis of breast surface temperature data collected automatically every 10 minutes shows how "strong" different rhythms are in the data. Cosine curves with trial periods ranging from 20 hours to 40 days were fitted by least squares to the data. The amplitude of each cosine curve (in ˚C) is represented by the height of each bar. The healthy left breast shows prominent rhythms with periods of about 1 day, 1 week and one perhaps corresponding to the woman's about 29-day menstrual cycle. As seen from the scale at the left, the about 24-hour rhythm has an amplitude of 1.4˚C (corresponding to a predictable change of over 2˚F above and below the average every day). The cancerous right breast shows weaker rhythmicity in general, no rhythm that is synchronized to 24-hour environmental cycles and rhythms that appear to be multiples of a 21-hour circadian component or submultiples of a 1-week synchronized circaseptan cycle.

At first the finding of an about 21-hour component in breast surface temperature by comparison to the usually 24-hour synchronized circadian rhythm, also found over the healthy breast, may appear to be a desynchronization, possibly a free-running rhythm. Contrary to this interpretation is the observation that most components found to be different from 24 hours, perhaps as an eigenfrequenz, are longer rather than shorter than 24 hours. Alternatively, a period of 21 hours can indicate a frequency-multiplied 42-hour component, which in turn may be a frequency-multiplied 84-hour cycle, both found over the cancerous breast. Moreover, the 84-hour component is a frequency-multiplied weekly (168-hour) cycle, seen over the healthy breast, along with a 24-day. Thus the question arises whether one deals in this cancer with a frequency demultiplication of a desynchronized circadian rhythm or with a frequency multiplication of the no longer present weekly rhythm, or even more broadly with a spectral compromise among the concomitantly assessed spectral components interacting with each other, with the 21-hour component being a compromise between wrangling 42-hour and 84-hour cycles, the latter a frequency-multiplied 168-hour (circaseptan) component that may in turn represent the "give" of about 4-week cycles. This case documents how two circadian components can coexist in the same body, one in a healthy breast, the other in a diseased breast, one perhaps documenting the coexistence in a bilateral organ such as the breast of a 24.0-hour synchronized systemic dominance while the diseased breast shows the prevalence of partly local diseased mechanisms.

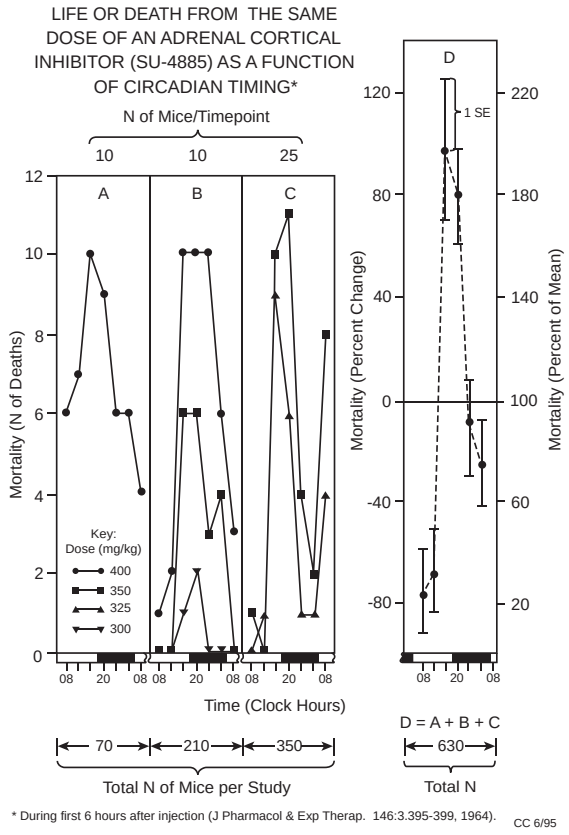


Fig. (3). Circadian susceptibility resistance cycle to SU-4885. © Halberg.

misconception that a calorie is a calorie whether consumed at breakfast or at dinner, yet to be revised, Fig. (**1**) [3, 4], in view of marked differences as a function of circadian stage documented in the use of calories, can be aligned with the demonstration that timing the limited daily access to food can account for the difference between life and death in the laboratory [43], Fig. (**3**). The relative body weight gain vs. loss, in a clinical center, when subjects are offered a fixed number of calories either as breakfast or as dinner [1, 2, 4] involving a different endocrine system [2, 4] needs to be explored along the scale of infradian cycles.

WHY SALIVA?

Longitudinal data, serially dependently collected around the clock over decades by a few motivated persons, have served many uses. They are products of a cartography of time structures of interest in their own right. Possible mechanisms underlying cycles found by transverse studies including, among others, variables of blood or urine, have also been mapped. Albeit no longer a widely used clinical endpoint, in the want of more contemporary determinations, a 15-year series with only a few missing urine samples suffices to uniquely reveal a set of cycles in the total daily excretion of steroidal breakdown products, the 17-ketosteroids (17-KS). Among others, cycles are detected with periods of about a half-week (circasemiseptan), a week (circaseptan), two weeks (diseptan), other multiples or submultiples of the week (multiseptans), a month (circatrigintan), 5 months (cis-half-year), a half-year (circasemiannual), a year (circannual), and with periods longer than a year by a few days (near-transyear) or a few months (far-transyear), as well as with periods of about 10 years (paradecadal). Near- and far-transyears have periods that are statistically significantly longer than the precise calendar year, their 95% confidence interval (CI) not overlapping 365.25 days. These newly discovered cycles in variables pertinent to the clinical chemical laboratory are statistically significantly different from circannuals, the latter defined as components with a period's CI overlapping the precise year. The many novel infradian cycles more generally are a challenge to medicine, as are multiple coexisting circadian components, each with a period between 20 and 28 hours. Coexisting multiple components are resolvable when certain time series reach an appropriate length, as now documented in data collected in health on a self-selected routine [44] and in illness [45]. As to the latter, results on saliva led to a novel laboratory diagnosis of multiple circadian ecfrequentia in the case of a woman (JF) with a twice-yearly adynamic depression. Among others, her blood pressure recordings served as markers of timing for carrying out and interpreting laboratory determinations in saliva, Figs. (**4 A**-**I**).

These results on salivary determinations cannot be approximated by clock-hour-specified single samples that fail to assess temporal variability. The story of the refinement of the diagnosis of steroidal rhythms in urine is presented as a challenge to introduce the socially less unacceptable saliva (as compared to blood or urine) more broadly into laboratory medicine. Above all, salivary determinations can guide cancer treatment which must not fly blind to various susceptibil-

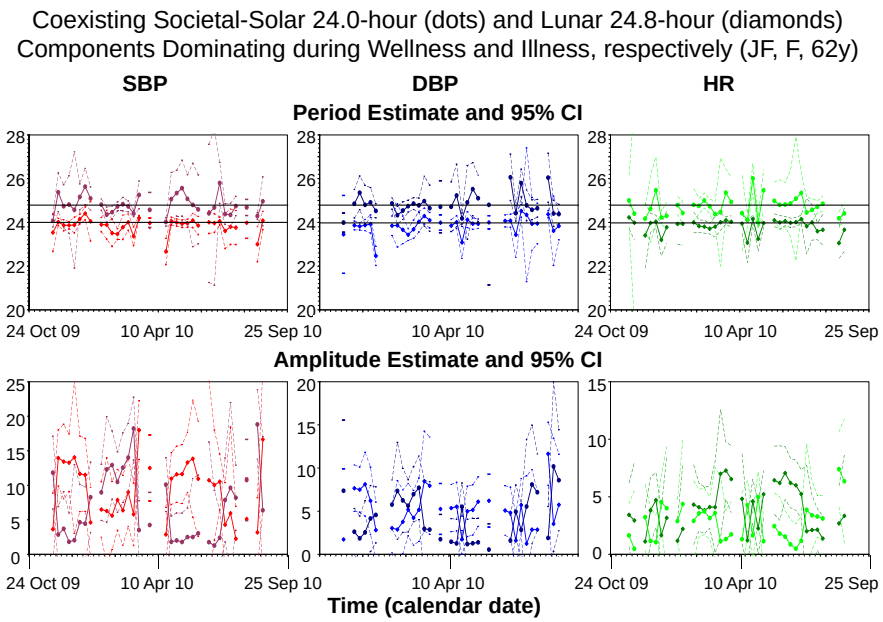
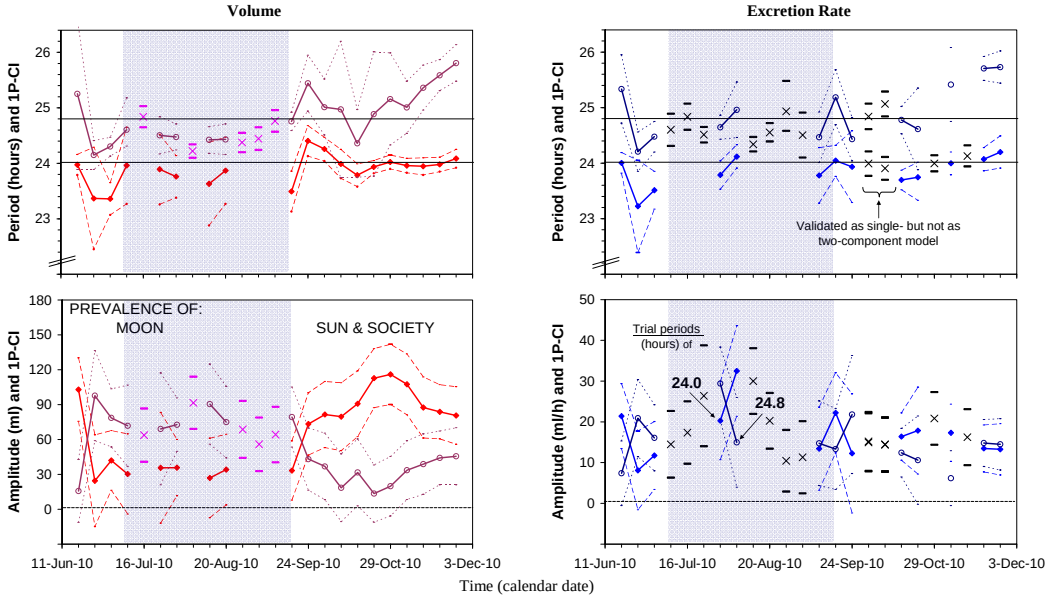


Fig. (4A). Around-the-clock data on systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) of a seleno-sensitive woman (JF) suffering from episodes of adynamic depression recurring twice a year and lasting 2-3 months were analyzed by the extended cosinor to assess the presence of a 24-hour synchronized circadian rhythm and of a desynchronized circadian component assuming a period close to 24.8 hours, the double tidal period. The two components with trial periods of 24 and 24.8 hours were fitted concomitantly by nonlinear least squares to data in a 4-week interval progressively displaced by 1 week throughout the entire time series. Point and 95% confidence intervals of the periods (top) and their corresponding amplitudes (bottom) are plotted as a function of time. During episodes of adynamia, the about 24.8-hour component is more prominent, whereas during wellness, the 24-hour synchronized component assumes the largest amplitude. © Halberg.

Mostly Present Lunar Wrestling with Solar-Societal Schedule in Urine Volume (left) and Urinary Excretion Rate (right) of Woman (JF, 62y) with Depressive Adynamia Lasting 2-3 Months, Recurring Twice a Year *



* with thus documented seleno-sensitivity, detected by the concomitant nonlinear fit of a 2-component model consisting of cosine curves with trial periods of 24.0 (filled diamonds) and 24.8 (open circles) hours to data in a 4-week interval displaced by 1 week, yielding estimates for each period (top) and corresponding amplitude (bottom), shown with their 1-parameter confidence intervals (1P-CI) derived by Marquardt's algorithm. Some 95% conservative confidence intervals of the amplitude also do not cover zero (not shown). Parameters could not be estimated in some intervals because model was then reduced to single major component (crosses).

Fig. (4B). Results similar to those of blood pressure and heart rate (see Fig. **4A**) are found for urine volume and urinary excretion rate. Results are shown with 1-parameter confidence intervals in view of the longer sampling interval for urine collections by comparison to the automatically measured blood pressure and heart rate data collected at hourly intervals around the clock. © Halberg.

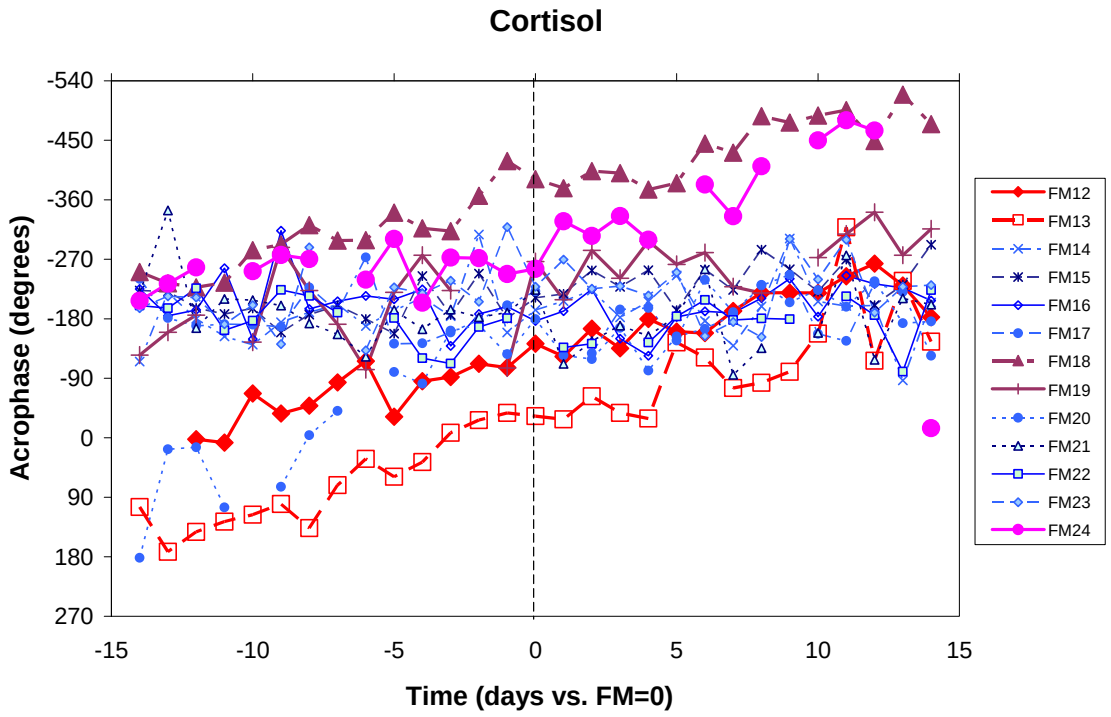


Fig. (4C). Time course of 24-hour acrophases for two weeks before (-1 to -15 days) and two weeks after (+1 to +15 days) the full moon (=0) determined from around-the-clock salivary determinations of cortisol of JF. The pull of the tides lengthens the dominant period during adynamic depression (red curves), whereas during wellness, the period is closer to but still slightly longer than 24 hours (blue curves). The period is calculated from changes in the 24-hour acrophases plotted as a function of time, centered on full moon for each lunar month. © Halberg.

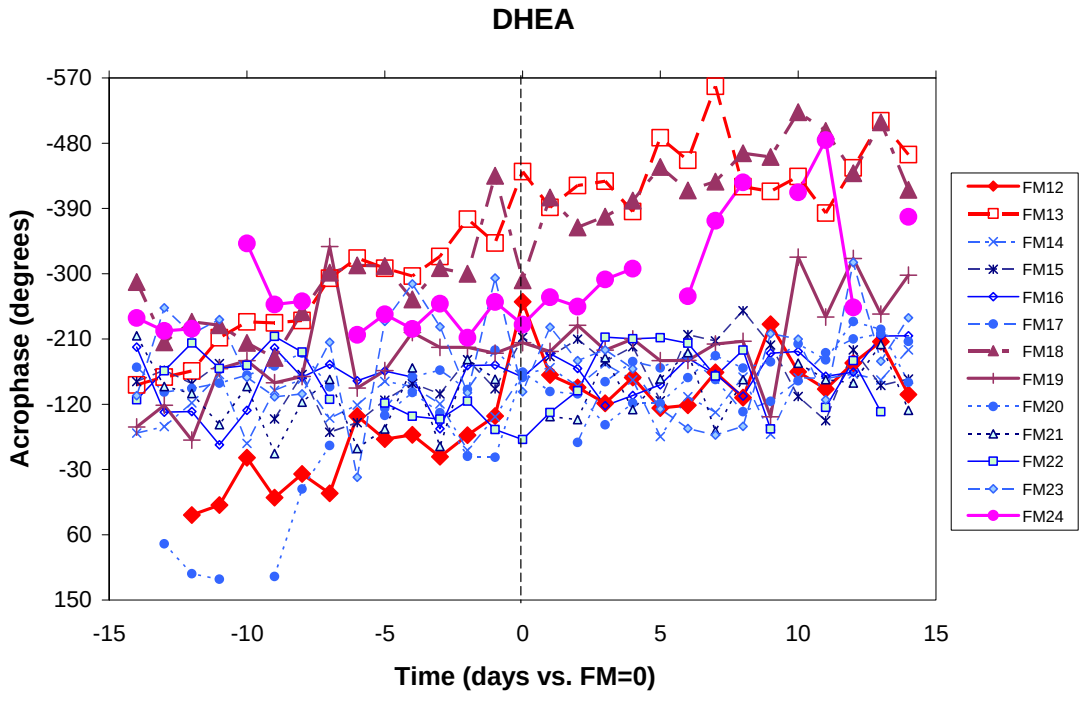


Fig. (4D). Time course of 24-hour acrophases for two weeks before (-1 to -15 days) and two weeks after (+1 to +15 days) the full moon (=0) determined from around-the-clock salivary determinations of DHEA of JF. The pull of the tides lengthens the dominant period during adynamic depression (red curves), whereas during wellness, the period is closer to but still slightly longer than 24 hours (blue curves). The period is calculated from changes in the 24-hour acrophases plotted as a function of time, centered on full moon for each lunar month.. © Halberg.

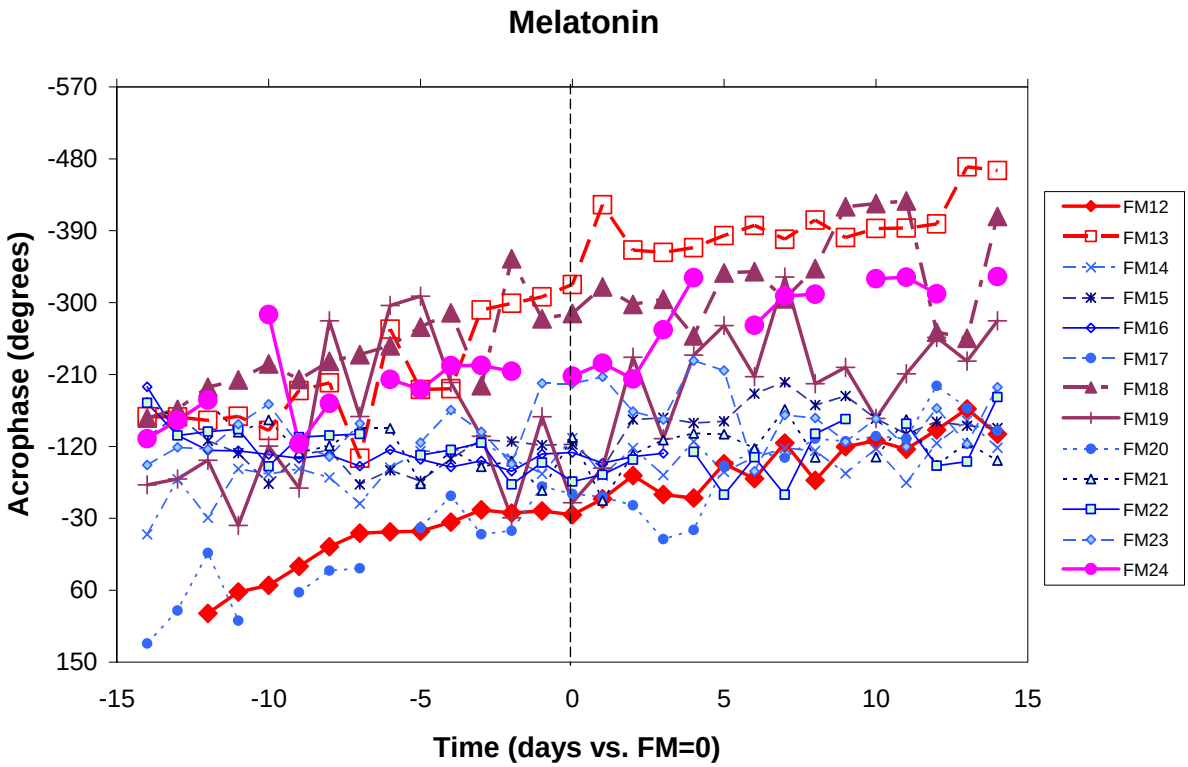


Fig. (4E). Time course of 24-hour acrophases for two weeks before (-1 to -15 days) and two weeks after (+1 to +15 days) the full moon (=0) determined from around-the-clock salivary determinations of melatonin of JF. The pull of the tides lengthens the dominant period during adynamic depression (red curves), whereas during wellness, the period is closer to but still slightly longer than 24 hours (blue curves). The period is calculated from changes in the 24-hour acrophases plotted as a function of time, centered on full moon for each lunar month. © Halberg.

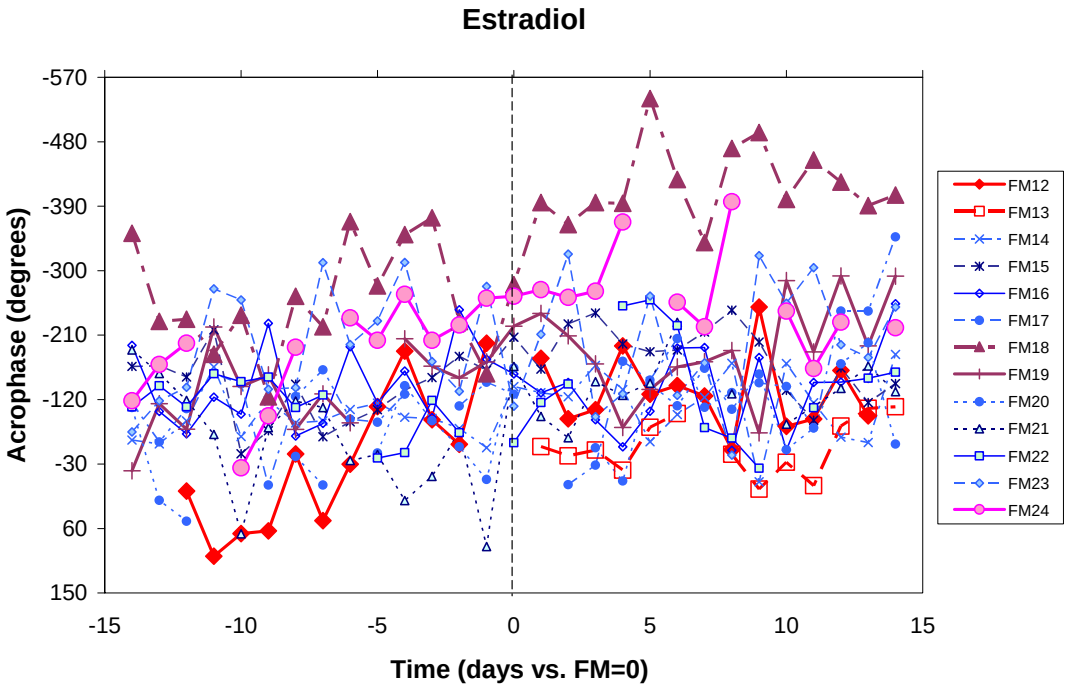


Fig. (4F). Time course of 24-hour acrophases for two weeks before (-1 to -15 days) and two weeks after (+1 to +15 days) the full moon (=0) determined from around-the-clock salivary determinations of estradiol of JF. The pull of the tides lengthens the dominant period during adynamic depression (red curves), whereas during wellness, the period is closer to but still slightly longer than 24 hours (blue curves). The period is calculated from changes in the 24-hour acrophases plotted as a function of time, centered on full moon for each lunar month. © Halberg.

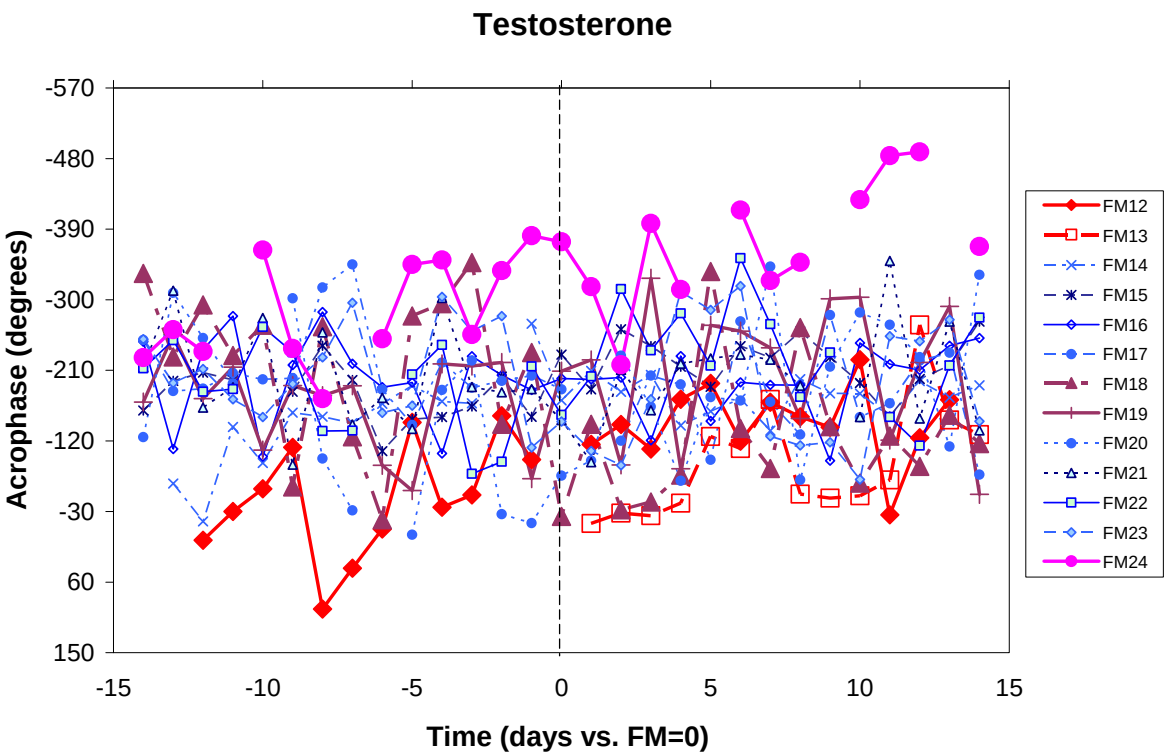


Fig. (4G). Time course of 24-hour acrophases for two weeks before (-1 to -15 days) and two weeks after (+1 to +15 days) the full moon (=0) determined from around-the-clock salivary determinations of testosterone of JF. The pull of the tides lengthens the dominant period during adynamic depression (red curves), whereas during wellness, the period is close to 24 hours (blue curves). The period is calculated from changes in the 24-hour acrophases plotted as a function of time, centered on full moon for each lunar month. © Halberg.

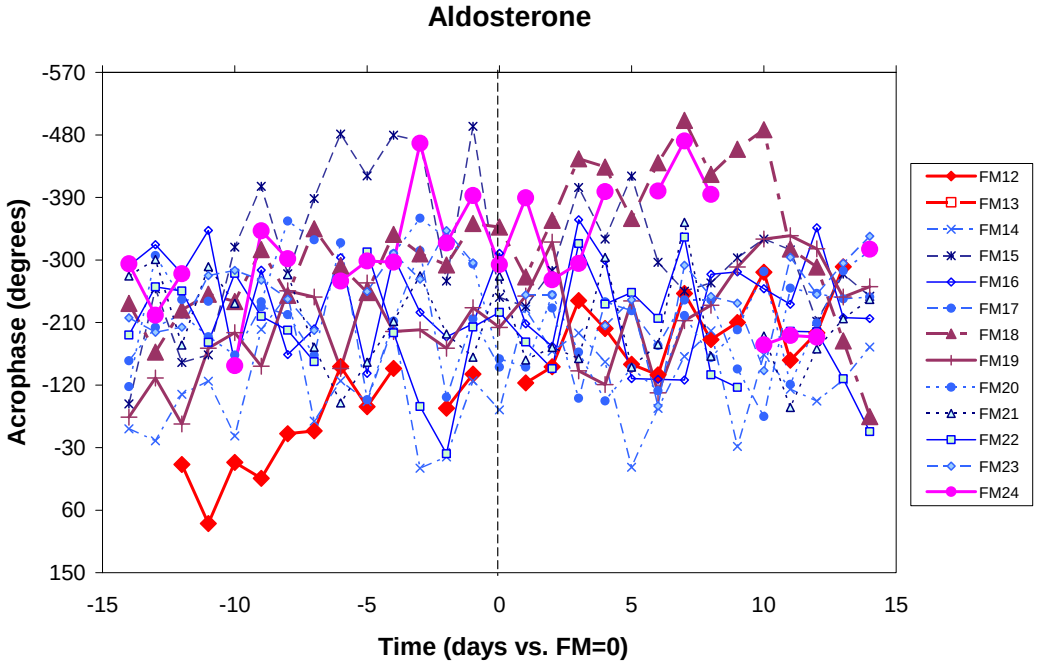


Fig. (4H). Time course of 24-hour acrophases for two weeks before (-1 to -15 days) and two weeks after (+1 to +15 days) the full moon (=0) determined from around-the-clock salivary determinations of aldosterone of JF. The pull of the tides lengthens the dominant period during adynamic depression (red curves), whereas during wellness, the period is close to 24 hours (blue curves). A desynchronized time course of 24-hour acrophases present during adynamic depression is not seen in aldosterone during wellness, presumably because of selective synchronization by twice-daily spironolactone. The period is calculated from changes in the 24-hour acrophases plotted as a function of time, centered on full moon for each lunar month. © Halberg.

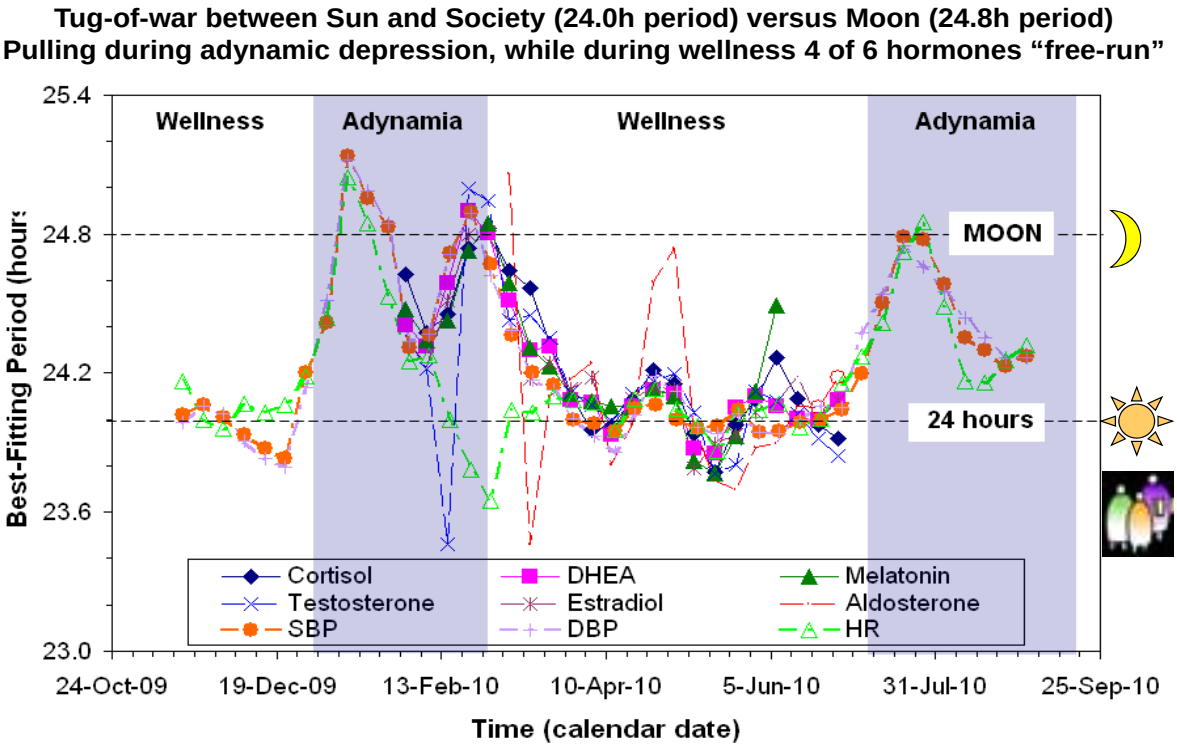


Fig. (4I). Wrangling between the moon on the one hand and society/sun on the other hand is seen in JF's endocrines as in her circulation, with the pull of the tides lengthening the dominant period during adynamic depression (shaded areas). In this graph, single component models were fitted nonlinearly, using trial periods of 24 or 24.8 hours. Results from the model accounting for the largest proportion of overall variance in a given 4-week interval (dot) are plotted. © Halberg.

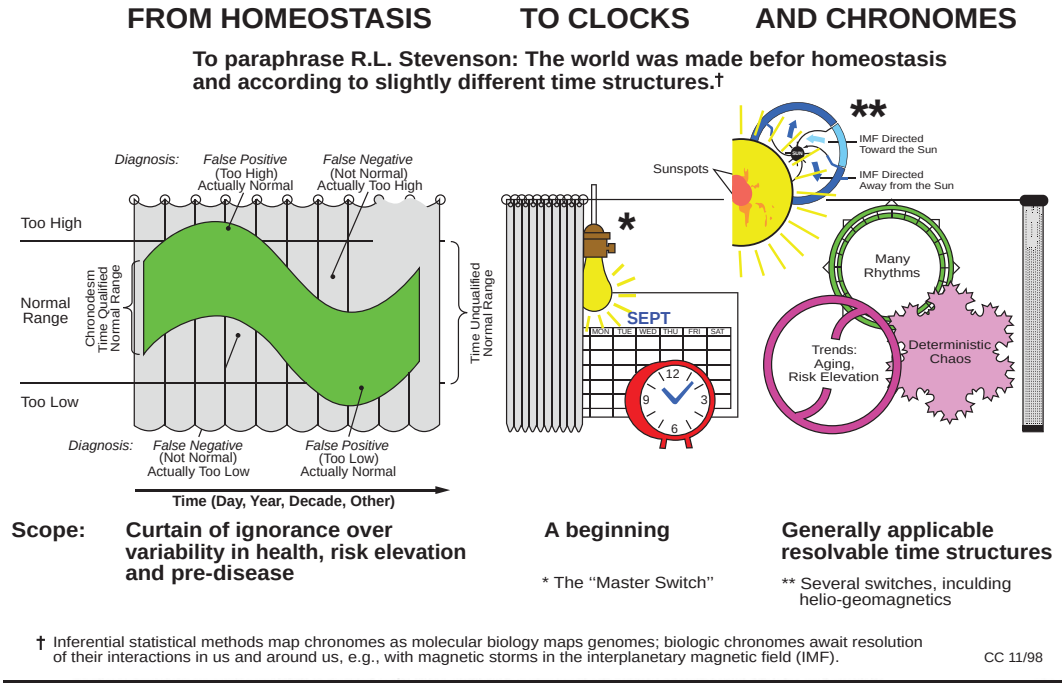


Fig. (5). Clocks and calendars (middle) only partly open the curtain of ignorance closed by concepts like homeostasis (left) over the entire range of physiological variation, ignoring structures consisting of deterministic and other chaos, trends and the many rhythms other than circadian and circannual components in this range in us and around us, some of the latter also built into us so that there are selective interactions among some already-mapped coperiodisms in the biosphere and its environment (right). © Halberg.

ity-resistance rhythms in the cancer, in the host and in the modulating environment, all affecting drug efficacy and toxicity [46].

More broadly, infradian rhythms relate not only to various aspects of physiology but also to sudden cardiac death [47, 48], suicide [49-52] and terrorism [53], associations that must all be explored from a clinical chemical viewpoint with respect to nutrition. Research topics today may lead to laboratory diagnoses tomorrow, as soon as we realize that circadian characteristics, rather than single daily samples, are a sine qua non for investigating infradians, e.g., in studies on aging, or on anything else along the scale of days to decades, if blunders are to be avoided, and that extra-circadians not only matter, but also that a budding atlas on infradians is in the making [54]. This atlas already has maps of decadal and multidecadal cycles that almost certainly reflect that we not only live in alternating light and darkness but are and have been exposed to the cycles of the sun along billions of years that are mirrored by cycles in our blood circulation, some of a length approximating human lifetimes [6].

SPECTRUM TO BE ASSESSED

Infradian temporal variability in human blood was mapped along with blood pressure monitoring on longitudinally studied individuals [55] before a new set of para-annual cycles differing from those of a year and a half-year length was discovered, as well as decadal and multidecadal cycles, also in variables of clinical chemical interest [6]. The data on blood [55] constituted a first step to assess the photic circadian and circannual rhythms and an about-monthly cycle. They were collected and interpreted originally as a lead to develop sampling schemes that may assess various disease risks by targeted multivariable sampling at different times after awakening in different seasons of a different assortment of various hormones [56]. The discovery of added novel components, mimicking the behavior of periods recorded in solar wind speed (SWS) [6], adds complexity. It could also refine the aim of defining earliest alterations of the endocrine system as a function of increased vascular and other disease risks [6].

These cycles constitute a broad spectrum of rhythms with similar frequencies in and around us, i.e., coperiodisms, characterizing inorganic, biotic and even noetic matter [6]. Cycles have been part of our endeavors in Minnesota leading to chronobiology and chronomics, Tables **1** [57] and **2** [54, 58-60]. Relatively high frequencies are found in electroencephalograms and electrocardiograms and very low ones in species diversity on the ocean floor [61]. Some of the cycles can be assessed in a human lifetime and longer ones in populations. Infradians (with periods longer than 28 hours) complement and modulate circadians, to the point that in any study on aging carried out at a fixed time of day, opposite results can be obtained along the scale of decades in work done consistently at one or the other of two clock-hours, 12 hours distant, e.g., at a circadian peak or trough [62, 63]. The photic day and year are complemented by nonphotic cycles probably related to magnetism, gravitation and other mostly unseen variables, Fig. (**5**) (right), involving 1. deterministic and other chaos that can generate cycles; 2. trends that (in longer than the available time series) can be part of a cycle longer than the series; and 3. the cycles themselves. We advocate analyzing the longest available time series as a whole (globally in time), to obtain all structural elements such as trends and cycles, followed by examining major rhythmic components (validated by the nonlinearly extended cosinor) in serial sections of the same series, using an interval that is systematically varied in length (locally in time), while similar time series are sought from different geographic locations, so that the desire to "think globally and act locally" is placed on a numerical spatio-temporal conceptual and methodologic glocality [62-65].

In all of these endeavors, routinely monitored marker rhythms are desirable [6, 65], and, of course, a marker rhythm is ideal when it is of interest in itself as an endpoint pertinent to a given problem such as MESOR-hypertension. Hence we recommend the routine clinical use of chronobiologically-interpreted long-term around-the-clock automatic ambulatory blood pressure and heart rate monitoring (C-ABPM) that serves multiple purposes in its own right while concomitantly exploring the circadian and infradian range for targeted broader sampling by the clinical chemist. Thereby, one can assess the impact of loads (stress), an opportunity that could be of interest to everybody [66]. As a measure of strain, routine C-ABPM detects circadian Vascular Variability Anomalies (VVAs) during 24-hour subspans of a 7-day record analyzed by the fit of a 24-hour cosine curve to the 7-day record as a whole and to separate 24-hour sections. The fit to the longer record smoothes transient abnormalities limited to a few days. In the separately analyzed 24-hour records, 1-day VVAs are detected before they become undue, potentially harmful strain as Vascular Variability Disorders (VVDs), defined as VVAs persisting in consecutive 7-day records, in the absence of a known physical or emotional load. Treating VVAs and VVDs means treating risk, whether these abnormalities are only markers or actual contributors to disease (they are likely both, [6]). The VVDs in C-ABPM also constitute harbingers of severe disease. Pertinent to the topic herein, advocating C-ABPM as a routine is a dividend: C-ABPM can guide the timing of sampling of human blood, urine and saliva.

Elsewhere ([45], see also Figs **4A-I**), we use a case report as a model that should lead, whenever possible, to saliva collection, rather than to studies dealing primarily with blood, to explore, among others, the chemical basis of a set of novel diagnoses of VVAs and other variability anomalies. These should be detected by human monitoring, complemented by as-one-goes analyses in systematically carried-out repeated passes over the accumulating physiological data [67], as has already been done for decades around the clock on some test pilots starting in adulthood [6, 65], and in one case starting at birth [68].

We aim at an international website [65], perhaps as a cloud system, also receiving epidemiological and sociological information from health and police departments on an international scale to align physiology with natality, morbidity, mortality and criminality as well as terrorism, i.e., with individual and societal pathology. Sooner or later, information obtained in cartography by such a system will have to replace the current imaginary "baselines", "secularities" and "normal ranges", realizing that variability within the physio-

Table 1. Minnesota Contributions Leading to Chronobiology (Annu Rev Physiol 1969; 31: 675-725) Resolving Biological Time Structures, Including Circadian (Z Vitamin-, Hormon-u Fermentforsch 1959; 10: 225-296) and Other Rhythms

1. The partly **genetic basis of circadian rhythm** characteristics and their uncertainties initially documented by differences in extent of within-day change of circulating eosinophil cell counts, among inbred strains of mice (1950) (Proc Soc exp Biol 1950; 75: 846-847) and by **periods in core temperature, differing from their environmental 24-hour counterparts** after blindness, "free-running" (Am J Physiol 1954; 179: 229-255). Human hereditary aspects of about (~) 24-hour and ~7-day cycles documented on twins (Biomedicine & Pharmacotherapy 2001; 55 [Suppl 1]: 32s-50s).

2. The importance of the **adrenal cortical cycle:** documented by a **"remove"** (and replace) **approach** (1951: Journal-Lancet [Minneapolis] 1951; 71: 312-319; Journal-Lancet [Minneapolis] 1953; 73: 20-3; Postgrad Med 1958; 24, 349-3582).

3. **Light and feeding schedules**, competing environmental **synchronizers** of circadian rhythms, mealtime dominating on a restricted diet (1953: Am J Physiol 1953; 174: 109-122).

4. Timing in the cell: RNA and DNA are strongly circadian periodic; **RNA synthesis precedes DNA formation** in the cell cycle, describing what really happens in time in cellular transcription. Also, that a rhythm in cell membrane phospholipid peaks before RNA formation (1958; Proc Soc exp Biol (NY) 1958; 97, 897-900). First hint that RNA may also precede DNA in evolution.

5. Importance of **hypothalamus** traced from the eyes as transducers of lighting regimen effects on circadian period of adrenal cortex over the pituitary to the CNS (1954: In: Withrow RB, editor. Photoperiodism and Related Phenomena in Plants and Animals. Ed. Publ. No. 55. Washington DC: AAAS; 1959. p. 803-878; many subsequent articles) and to the **cell**. The suprachiasmatic nucleus, part of the hypothalamus, was identified later, and its then-claimed importance as sole timer was debunked by 1958 and subsequently (Chronobiologia 1979; 6: 405-424; Anat Rec 1974; 180: 47-52). The long-denied timing mechanisms in the periphery, denied for decades, are also now accepted.

6. **Timing for the body as a whole:** different, including opposite effects of the same hormones (growth hormone, ACTH, TSH) or (e.g., anti-cancer) drugs, or of the same number of calories, depending only on the circadian timing of administration (1973; Experientia [Basel] 1973; 29: 909-934; Peptide chronomics. In: Kastin A, editor. Handbook of Biologically Active Peptides. Amsterdam: Elsevier; 2006. p. 1529-1564).

7. **Circadian rhythms tip the scale between life and death** in response to many stimuli: physical stimulus (noise) (1955: Proc Soc exp Biol (NY) 1955; 88: 169-173); whole-body irradiation (Haus E, Halberg F, Loken MK, in Scheving LE, Halberg F, Pauly JE eds. Chronobiology, Proc. Int. Soc. for the Study of Biological Rhythms, Little Rock, Ark. Stuttgart: Georg Thieme Publishers/Tokyo: Igaku Shoin Ltd.; 1974. p. 115-122); chemical (alcohol) (J appl Physiol 1959; 14, 878-880); biochemical (endotoxin) (J clin Endocrinol 1955; 15: 887); drug (ouabain) (Fed Proc 1959; 18: 63), culminating in the doubling of the 2-year survival rate in patients with advanced perioral cancers (Guest Lecture, Proc. 30th Ann. Cong. Rad., January 1977, Post-Graduate Institute of Medical Education and Research, Chandigarh, India, 8 pp; J Exp Therapeutics Oncol 2003; 3: 223-260).

8. **Circadian rhythmicity in a prokaryote** (without a nucleus), originally strongly contradicted by a committee on the molecular basis of circadian rhythms (Report of the Dahlem Workshop on the Molecular Basis of *Circadian Rhythms, Berlin, November 3-7, 1975. Berlin: Dahlem Konferenzen, 1976: 462 pp); that partly endogenous rhythms are found in all life (Proc MN Acad Sci 1961; 29: 227-239) is now universally accepted.

9. **A broad set of statistical methods and programs** for detecting, validating, quantifying and comparing (always with uncertainties estimated) rhythms, trends and chaos starting with the linear and nonlinear **cosinor** (in von Mayersbach H, ed. The Cellular Aspects of Biorhythms, Springer Verlag, NY, 1967, pp. 20-48; cf. Acta med rom 1980; 18: 399-440).

10. Discovery of an (eventually long) list of periods in addition to about-daily (circadian) periods, starting with the **biological near-week**, followed by discovery of the corresponding **geomagnetic near-week** followed by numerous other infradian periods (1965: Acta endocrinol 1965; 50 [Suppl 103]: 5-54; University of Minnesota/Medtronic Chronobiology Seminar Series, #1, December 1991), leading from chronobiology, a figurative microscopy in time, to chronomics, a figurative telescopy in time.

Table 2. Minnesotan Contributions to Chronomics, Resolving Transdisciplinary Geo-bio-noospheric Coperiodisms Leading to a Unified Science and Art* (Biomed & Pharmacother 2004; 58 [Suppl 1]: S150-S187)

1. A set of methods and programs resolving, with uncertainties, coexisting multiple, sometimes spectrally neighboring periods, τ, with non-overlapping CIs (95% confidence intervals) of τ, revealing and mapping non-stationarity in time and space (including the transient disappearance of an aeolian nonphotic component in certain spectral or geographic locations).

2. **Congruences** defined by overlapping CIs of period, τ, and/or phase, ϕ, e.g., within the organism (division of labor in time), within the environment (e.g., Kp vs. Wolf numbers, geo- vs. heliomagnetism) or external-internal congruences (e.g., blood pressure and geomagnetism) at a given τ

3. **New internal-external congruent CIs of τs define coperiodisms**, some found first in living matter and next in the abiotic environment, others vice versa, constituting a transdisciplinary spectrum with component τs of **a near-week, an about (~) 2-week, ~1-month, ~5-month (quinmensal), semiannual, circannual, near- and far-transannual, diennian, septennian, decadal, ~15-17-year, paradecadal, paradidecadal, paratridecadal (BEL, Bruckner-Egeson-Lockyer, near 30-40-years), ~50-year (semicentennian), transsemicentennian, semimillennian and myriadennian components**

Table 2. Contd….

4. Partial endogenicity, **genetic coding** supported by τs with nonoverlapping CIs in and around us (free-run), and by "after single stimulus" manifestation ("induction")

5. Brain (pineal and suprachiasmatic nucleus, SCN) (mediating) or heart, circulation and cell (reflecting) non-photic environmental effects (shown by SCN ablation or magnetic storm effects)

6. Nonphotic spectral components in populations of **eukaryotes and prokaryotes** (decadals in bacterial mutations)

7. **Selective assortment (SA)** of τs (or ϕs) among and within individuals, in organ systems, variables, cycle characteristics (MESOR vs. amplitude), and in their lock-ins (of ϕ, e.g, of 17-ketosteroids with Kp and urine volume not with Kp but possibly with Wolf numbers)

8. **SA** of τs in different variables of the same population or of phases at a fixed τ in different populations

9. Nonphotics can tip the scale between little or none versus many **infections**, **sudden cardiac death**, **suicide** and **terrorism**

10. Odds ratios for the number of shared frequencies between human mental functions and either helio- or geo- magnetism more than match the association of helio- and geo-magnetism to each other

*Rules learned from decades-long longitudinal studies of populations and of individuals analyzed **glo**bally and lo**cal**ly, **glocally in space and time,** as a method as well as a map, updated **progressively** at intervals determined by the cycles detected **and pergressively** surveilled in serial sections and their sequential analysis in repeated passes over the accumulating data for resolution of changes in characteristics of each cycle in individuals, eventually from womb to tomb and in populations beyond the human lifespan

Choices in dealing with respect to personal, societal (human-made) and natural disasters

1) We currently try, but may not be able, to respond to each cataclysm after it occurs, whether it is a massive stroke, a crime, a terrorist attack or an earthquake;

2) we can assess currently conventional risk factors and try to reduce their impact according to visits with a care provider, but fly blind with respect to vascular and other variability disorders that cannot be detected by a single or 24-hour spotcheck, or **alternatively**

3) the individual and society can survey the time structure of personal health by, first, vascular monitoring and society can implement a system using the physiological data aligned with those from epidemiological and social monitoring, with the tools of a temporal microscope (chronobiology) and telescope (chronomics), to assess one's position by comparing a personalized with a corresponding gender-age-ethnicity-matched chronousphere providing reference standards as glocal maps via an international website

Of particular interest are **far-transyears**, mostly between 1.2 and 1.9 years, which drift in frequency or phase and wax and wane in amplitude to the point of disappearance and reappearance. So do **near-transyears**, longer than 1 year but shorter than 1.2 years, found **after their detection in biology** in solar and terrestrial **magnetism** and other counterparts, just as we found the **geomagnetic** near-week in Kp, validated by Roederer and extended to aa by Vladimirsky as a counterpart to a set of biological near-weeks, most of which differ from precisely one week and may hence be partly built-in.

logical range can provide useful information regarding health and disease risk. Instead, any intervention is best assessed by testing for any deviation from the stages of various cycles involved along the time scale of a given problem. Maps of the cycles' characteristics could become the ongoing reference standard and used with sequential (inferential statistical) analyses, such as cumulative sum (CUSUM) control charts [69], applied to the individual, to detect changes that call for intervention by the individual and/or by society, as also advocated by others [70].

The biography and bibliography of Douglas Wilson, kindly provided by him, that follow, demonstrate, better than any words, his contributions specifically to salivary investigations and more broadly to chronobiology and chronomics, tools of a unified culture, whereby transdisciplinary sciences and the arts are united by a common time structure, the chronousphere [6].

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

This work was supported by NIH grant GM-13981 (FH) and by the University of Minnesota Supercomputing Institute (GC, FH).

REFERENCES

[1] Halberg F. From aniatrotoxicosis and aniatrosepsis toward chronotherapy: Introductory remarks to the 1974 Capri Symposium on

timing and toxicity: the necessity for relating treatment to bodily rhythms. In: Aschoff J, Ceresa F, Halberg F. Eds. Chronobiological Aspects of Endocrinology. Stuttgart: F.K. Schattauer Verlag 1974; pp. 1-34.

[2] Graeber RC, Gatty R, Halberg F, Levine H. Human eating behavior: preferences, consumption patterns and biorhythms. Technical Reports, NATICK/TR-78/022 U.S. Army, 1978; pp. 287.

[3] Halberg F, Haus E, Cornelissen G. From biologic rhythms to chronomes relevant for nutrition. In: Marriott BM, Ed. Not Eating Enough: Overcoming Underconsumption of Military Operational Rations. Washington DC: National Academy Press 1995; pp. 361-72. Available from: http://books.nap.edu/books/0309053412/-html/361.html#pagetop

[4] Cornelissen G. When you eat matters: 60 years of Franz Halberg's nutrition chronomics. Open Nutraceuticals J 2012; 5(Suppl 1-M2): 16-44.

[5] Halberg F, Visscher MB, Bittner JJ. Eosinophil rhythm in mice: Range of occurrence; effects of illumination, feeding and adrenalectomy. Am J Physiol 1953; 174: 109-22.

[6] Halberg F, Cornelissen G, Katinas GS, *et al*. Many rhythms are control information for whatever we do: an autobiography. Folia Anthropologica 2012; 12: 5-134. Available from: http://ttk.nyme.-hu/blgi/Knyvek%20kiadvnyok/FOLIA%20ANTHROPOLOGICA/folia12.pdf

[7] Halberg E, Halberg F, Haus E, *et al*. Toward a chronopsy: Part I. A chronobiologic case report and a thermopsy complementing the biopsy. Chronobiologia 1978; 5: 241-50.

[8] Halberg E, Halberg F, Cornelissen G, *et al*. Toward a chronopsy: Part II. A thermopsy revealing asymmetrical circadian variation in surface temperature of human female breasts and related studies. Chronobiologia 1979; 6: 231-57.

[9] Halberg E, Fanning R, Halberg F, *et al*. Toward a chronopsy: Part III. Automatic monitoring of rectal, axillary and breast surface temperature and of wrist activity; effects of age and of ambulatory surgery followed by nosocomial infection. Chronobiologia 1981; 8: 253-71.

[10] Simpson HW. Sir James Young Simpson Memorial Lecture 1995. Breast Cancer Prevention; a pathologist's approach. J R Coll Surg Edinb 1996; 41; 359-70.

[11] Gautherie M, Gros CH. Circadian rhythm alteration of skin temperature in breast cancer. Chronobiologia 1977; 4: 1-17.

[12] Gautherie M, Gros CH. Contribution of infrared thermography in early diagnosis, pre-therapeutic prognosis and post-irradiation follow-up of breast carcinomas. Med Mundi 1976; 21: 135-49.

[13] Halberg F, Bingham C. Chronobiology, a paradigm for biomedicine: personalized P-values for assessing health, risk, or disease. Proc. Am. Statistical Assn., Chicago, August 19-21, 1986; p. 136.

[14] Halberg F, Cornelissen G, Wilson D. N-of-1 or N-of-6 chronobiologic test pilots guide clinical trials in cardiology, endocrinology and oncology. Abstract, ISCB 13, Int. Soc. Clin. Biostatistics, Copenhagen, Denmark, Aug. 17-21, 1992; p. 54.

[15] Cornelissen G, Bingham C, Wilson D, Halberg F. Illustrating power of cost-effective "Phase 0" chronobiologic trials in endocrinology, psychiatry and oncology. Plenary lecture, 13th meeting Int. Soc. Clinical Biostatistics, Copenhagen, Denmark, August 17-21, 1992. In: Cornelissen G, Halberg E, Bakken E, Delmore P, Halberg F. Eds. Toward phase zero preclinical and clinical trials: chronobiologic designs and illustrative applications. University of Minnesota Medtronic Chronobiology Seminar Series, #6, September 1992; pp. 138-81.

[16] Halberg F. Chronobiologic perspectives in cardiovascular diseases. Abstract, Health of Inner Cities and Urban Areas, International Conference, Cardiff, Wales, September 4-7, 1989, The Institute of Statisticians/SIRMCE, 1989; p. 73.

[17] Cornelissen G. Challenge to the statistician interested in the individualized assessment of health in the inner cities and urban areas: a tribute to Franz Halberg. (Health of Inner Cities and Urban Areas, International Conference, Cardiff, Wales, September 4-7, 1989.) The Statistician 1990; 39: pp. 105-9.

[18] Halberg F, Cornelissen G, International Womb-to-Tomb Chronome Initiative Group. Resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation), Brussels, Belgium, March 17-18, 1995: Fairy tale or reality? Medtronic Chronobiology Seminar #8, April 1995; p. 12 text, 18 figures. Available at: http://www.msi.umn.edu/halberg/

[19] Halberg F, Bingham C, Siegelova J, *et al*. "Cancer marker chronomes" assessed in the light of chronobioethics. Chronobiologia 1994; 21: 327-30.

[20] Cornelissen G, Bingham C, Siegelova J, *et al*. Cardiovascular disease risk monitoring in the light of chronobioethics. Chronobiologia 1994; 21: 321-5.

[21] Halberg F, Cornelissen G, Wilson D, *et al*. Chronobiology and chronomics: detecting and applying the cycles of nature. Biologist 2009; 56(4): 209-14.

[22] Homolka P, Cornelissen G, Homolka A, Siegelova J, Halberg F. Exercise-associated transient circadian hypertension (CHAT)? Abstract, III International Conference, Civilization diseases in the spirit of V.I. Vernadsky, People's Friendship University of Russia, Moscow, Oct. 10-12, 2005; pp. 419-21.

[23] Joyce BG, Wilson DW, Read GF, Riad-Fahmy D. An improved enzyme immunoassay for progesterone in human plasma. Clin Chem 1978; 24: 2099-102.

[24] Walker RF, Wilson DW, Read GF, Riad-Fahmy D. Assessment of testicular function by the radioimmunoassay of testosterone in saliva. Int J Androl 1980; 3: 105-20.

[25] Campbell IT, Walker RF, Riad-Fahmy D, Wilson DW, Griffiths K. Circadian rhythms of testosterone and cortisol in saliva: effects of activity-phase shifts and continuous daylight. Chronobiologia 1982; 9: 389-96.

[26] Griffiths K, Read GF, Wilson DW. Breast cancer research: a new approach through assays for steroids in saliva. Thai J Surg 1983; 4: 49-58.

[27] Griffiths K, Read GF, Wilson DW, Fahmy DR. Breast cancer research: a new approach through assays for steroids in saliva. Rev Endocr-Relat Cancer 1983; Suppl 13: 45-53.

[28] Read GF, Fahmy DR, Wilson DW, Griffiths K. A new approach for breast cancer research: assays for steroids in saliva. In: Bulbrook RD, Taylor JD, Eds. Commentaries on Research in Breast Disease. vol. 3. New York: Alan R. Liss Inc.; 1983; pp. 61-92.

[29] Read GF, Wilson DW, Campbell FC, Holliday HW, Blamey RW, Griffiths K. Salivary cortisol and dehydroepiandrosterone sulphate levels in postmenopausal women with primary breast cancer. Eur J Cancer Clin Oncol 1983; 19: 477-83.

[30] Read GF, Wilson DW, Hughes IA, Griffiths K. The use of salivary progesterone assays in the assessment of ovarian function in postmenarcheal girls. J Endocrinol 1984; 102: 265-8.

[31] Wilson DW, Read GF, Hughes IA, Walker RF, Griffiths K. Hormone rhythms and breast cancer chronoepidemiology: salivary progesterone concentrations in pre- and post-menarchal girls and in normal premenopausal women. Chronobiol Int 1984; 1: 159-65.

[32] Campbell IT, Wilson DW, Walker RF, Griffiths K. The use of salivary steroids to monitor circadian rhythmicity on expeditions in the Arctic. Chronobiol Int 1985; 2: 55-9.

[33] Walker RF, Wilson DW, Truran PL, *et al*. Characterization of profiles of salivary progesterone concentrations during the luteal phase of fertile and subfertile women. Endocrinology 1985; 104: 441-6.

[34] Read GF, Bradley JA, Wilson DW, George WD, Griffiths K. Evaluation of luteal-phase salivary progesterone levels in women with benign breast disease or primary breast cancer. Eur J Cancer Clin Oncol 1985; 21: 9-17.

[35] Read GF, Hughes IA, Wilson DW, Griffiths K. Measurements of salivary progesterone concentrations as an index of corpus luteum function in adolescent girls. In: Venturoli S, Flamigni C, Givens JR, Eds. Adolescence in Females. Chicago: Year Book Medical Pub 1985; pp. 471-3.

[36] Kumar S, Mansel RE, Wilson DW, *et al*. Daily salivary progesterone levels in cyclical mastalgia patients and their controls. Br J Surg 1986; 75: 260-3.

[37] Read GF, Wilson DW, Bradley JA, George WD, Griffiths K. The hormonal etiology of breast disease: a new approach using the determination of salivary progesterone. In: Angeli A, Bradlow HL, Dogliotti L, Eds. Endocrinology of the Breast: Basic and Clinical Aspects. volume 464. New York: Annals of the New York Academy of Sciences 1986; pp. 573-5.

[38] Danutra V, Turkes A, Read GF, *et al*. Progesterone concentrations in samples of saliva from adolescent girls living in Britain and Thailand, two countries where women are at widely differing risk of breast cancer. J Endocrinol 1989; 121: 375-81.

[39] Walker RF, Read GF, Wilson DW, Riad-Fahmy D, Griffiths K. Chronobiology in laboratory medicine: principles and clinical ap-

plications illustrated from measurements of neutral steroids in saliva. Prog Clin Biol Res 1990; 341A: 105-17.
[40] Wilson DW, Walker RF, Read GF, Griffiths K. Potential value of salivary steroids in chrono-epidemiological and endocrine-related studies. Prog Clin Biol Res 1990; 341A: 119-30.
[41] Read GF, Walker RF, Wilson DW, Griffiths K. Steroid analysis in saliva for the assessment of endocrine function. In Castagnetta L, d'Aquino S, Labrie F, Bradlow HL, Eds. Steroid Formation, Degradation, and Action in Peripheral Tissues. vol. 595. New York: Annals of the New York Academy of Sciences; 1990; pp. 260-74.
[42] Wilson DW, Turkes A, Jones R, Danutra V, Read GF, Griffiths K. A comparison of menstrual cycle profiles of salivary progesterone in British and Thai adolescent girls. Eur J Cancer 1992; 28A: 1162-7.
[43] Nelson W, Cadotte L, Halberg F. Circadian timing of single daily "meal" affects survival of mice. Proc Soc Exp Biol (NY) 1973; 144: 766-9.
[44] Costella JF, Halberg F, Hillman D, Mikulecky M, Cornelissen G. Four circadian and two circasemidian periods in sleep-wakefulness of a man on a self-selected routine. Folia Anthropol 2012; 11: 51-3.
[45] Halberg F, Cornelissen G, Hillman D, *et al.* Multiple circadian periods in a lady with recurring episodes of adynamic depression: case report. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Noninvasive Methods in Cardiology. Brno, Czech Republic. Brno: Faculty of Medicine, Masaryk University. 2011; pp. 45-67.
[46] Halberg E, Cornelissen G, Haus E, *et al.* Amplification [on comments by Berry DA. Power of chronobiologic pilots: a statistician's opinion. Chronobiologia 1993; 20: 213-4. Chronobiologia 1993; 20: 214-8. [Erna test].
[47] Halberg F, Cornelissen G, Otsuka K, *et al.* Incidence of sudden cardiac death, myocardial infarction and far- and near-transyears. Biomed Pharmacother 2005; 59(Suppl 1): S239-61.
[48] Cornelissen G, Halberg F, Rostagno C, Otsuka K. A chronomic approach to cardiac arrhythmia and sudden cardiac death. Auton Nerv Syst 2007; 44: 251-4.
[49] Halberg F, Cornelissen G, Panksepp J, Otsuka K, Johnson D. Chronomics of autism and suicide. Biomed Pharmacother 2005; 59(Suppl 1): S100-8.
[50] Halberg F, Cornelissen G, Berk M, *et al*. Solar signatures in Australian suicide incidence: gender differences in prominence of photic vs. nonphotic spectral components. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Proceedings, Noninvasive Methods in Cardiology. Brno, Czech Republic, October 4-7, 2008; pp. 44-62. Available at: http://web.fnusa.cz/files/kfdr2008/sbornik_2008.pdf
[51] Cornelissen G, Halberg F. Chronomics of suicides and the solar wind. Br J Psychiatry 2006; 189: 567-8. Reply to Salib E, Cortina-Borja M. Effect of month of birth on the risk of suicide. Br J Psychiatry 2006; 188: 416-22.
[52] Cornelissen G, Dimitrov BD, Carandente F, Halberg F. Space and earth weather mirrored in patterns of suicide incidence. World Heart J 2011; 3: 31-42.
[53] Halberg F, Cornelissen G, Sothern RB, Katinas GS, Schwartzkopff O, Otsuka K. Cycles tipping the scale between death and survival (= "life"). Prog Theor Phys 2008; Suppl 173: 153-81.
[54] Halberg F, Cornelissen G, Otsuka K, Schwartzkopff O, Halberg J, Bakken EE. Chronomics. Biomed Pharmacother 2001; 55(Suppl 1): 153s-90s.
[55] Halberg F, Cornelissen G, Sothern RB, *et al*. International geographic studies of oncological interest on chronobiological variables. In: Kaiser H, Ed. Neoplasms -- Comparative Pathology of Growth in Animals, Plants and Man. Baltimore: Williams and Wilkins; 1981; pp. 553-96.
[56] Hermida Dominguez R, Del Pozo F, Halberg F. Endocrine chronorisk of developing breast cancer assessed individually by pattern recognition. Chronobiologia 1982; 9: 341-2.
[57] Halberg F. Chronobiology. Annu Rev Physiol 1969; 31: 675-725.
[58] Halberg F, Cornelissen G, Schack B, *et al*. Blood pressure self-surveillance for health also reflects 1.3-year Richardson solar wind variation: spin-off from chronomics. Biomed Pharmacother 2003; 57(Suppl 1): 58s-76s.
[59] Cornelissen G, Masalov A, Halberg F, *et al.* Multiple resonances among time structures, chronomes, around and in us. Is an about 1.3-year periodicity in solar wind built into the human cardiovascular chronome? Hum Physiol 2004; 30(2): 86-92.
[60] Halberg F, Cornelissen G, Regal P, *et al*. Chronoastrobiology: proposal, nine conferences, heliogeomagnetics, transyears, near-weeks, near-decades, phylogenetic and ontogenetic memories. Biomed Pharmacother 2004; 58(Suppl 1): S150-87.
[61] Cornelissen G, Bakken EE, Sonkowsky RP, Halberg F. A 38-million-year cycle among myriadennians in the diversity of oceanic genera. Abstract, III International Conference, Civilization diseases in the spirit of V.I. Vernadsky, People's Friendship University of Russia, Moscow, 2005; pp. 47-9.
[62] Halberg F, Sothern RB, Cornelissen G, Czaplicki J. Chronomics, human time estimation, and aging. Clin Interv Aging 2008; 3(4): 749-60. Available at : http://www.dovepress.com/articles.php?article_id=2608
[63] Watanabe Y, Cornelissen G, Refinetti R, *et al.* Cardiovascular monitoring at the South Pole reveals two simultaneous circadian components in blood pressure. Proceedings, International Conference on the Frontiers of Biomedical Science: Chronobiology, Chengdu, China, 2006; pp. 232-4.
[64] Halberg F, Cornelissen G, Hillman D, *et al*. Chronobiologically interpreted ambulatory blood pressure monitoring in health and disease. Glob Adv Health Med 2012; 1(2): 64-88.
[65] Halberg F, Cornelissen G, Gumarova L, *et al*. Integrated and as-one-goes analyzed physical, biospheric and noetic monitoring: Preventing personal disasters by self-surveillance may help understand natural cataclysms: a chronousphere (chrono-noösphere). London: SWB International Publishing House; 2012; p. 106.
[66] Halberg F, Cornelissen F, Halberg Francine, Kessler T, Otsuka K. Measuring mental strain by duration of blood pressure overswing (CHAT): case report. World Heart J 2010; 2(2): 141-67.
[67] Halberg F, Cornelissen G, Otsuka K, *et al.* Rewards in practice from recycling heart rate, ectopy, ischemia, and blood pressure in¬formation. J Med Eng Technol 1997; 21: 174-84.
[68] Watanabe Y, Nintcheu-Fata S, Katinas G, *et al*. Methodology: partial moving spectra of postnatal heart rate chronome. Neuroendocrinol Lett 2003; 24(Suppl 1): 139-44.
[69] Cornelissen G, Halberg F, Hawkins D, Otsuka K, Henke W. Individual assessment of antihypertensive response by self-starting cumulative sums. J Med Eng Technol 1997; 21: 111-20.
[70] Kasukawa T, Sugimoto M, Hida A, *et al*. Human blood metabolite timetable indicates internal body time. PNAS Early Edition 2012; p. 6. Available at: http://www.pnas.org/content/early/2012/08/22/-1207-768109.

Received: May 09, 2013 Revised: May 22, 2013 Accepted: May 22, 2013