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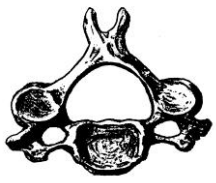

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CONTENTS

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MANY RHYTHMS ARE CONTROL INFORMATION FOR WHATEVER WE DO: AN AUTOBIOGRAPHY[1,2]

Franz Halberg (FH),
with Germaine Cornélissen, George S. Katinas, Dewayne Hillman, Kuniaki Otsuka, Yoshihiko Watanabe, Jinyi Wu, Francine Halberg, Julia Halberg, Mary Sampson, Othild Schwartzkopff and Erna Halberg+

Dedicated, as are all my endeavors, to the memory of my father Dr. Julius HALBERG to Dr. Walter NELSON, with thanks for a lifetime of his cooperation, and to the memory of his mentor Cyrus P. BARNUM, professor of biochemistry and, in his time, a leading specialist in nucleic acids. When FH asked the strait-laced Barnum for a technician's help with DNA and RNA determinations to map anticipated changes along the 24-hour scale, he replied that the idea of periodicity in nucleic acid – then deemed the most constant of living matter – was so unexpected that he felt he could not assign help paid from a government grant (his technicians were supported by NIH). It made sense to him, however, that if mitoses are periodic, so DNA and RNA should be as well. He replied "I'll be your technician"; a better tech could not have been found.

[1] In approaching any problem, stress and strain in particular, it is tempting to use a "norm" as an initial single value or a daily or yearly average, and to refer to it as a "baseline". Nearly 60 years ago, FH wrote (25), citing Zbigniew Z. Godlowski (J. Endocrinol 1952; 8: 102): "… it is not surprising to encounter reference to 'the great variation in circulating eosinophil counts, even in normal conditions, which makes it impossible to establish a base-line' for the study of the physiopathology of these cells. It is indeed impossible to establish a base-line, at least a straight base-line, for eosinophil counts in normal conditions, because there is none in normal conditions." Nor are there baselines for other variables, except in the wishful thinking of too many investigators, including the best, such as Hans Selye, as we will demonstrate. As of March 2012, 63,740 publications referring to "circadian" attest to the ubiquity of these variations; there are many extracircadian changes as well, all constituting control information to anything we do along the scale of time. We appeal to all authors and editors to debunk "baselines", and to use, whenever available, historical and concomitant controls in science (and art, most broadly in all "humanities").

[2] An earlier paper by FH was labeled by the editor of the Journal of Gerontology A: Biological Sciences and Medical Sciences "Future history" (169). This title applies to this historical sketch; it ends as an implied, here explicit recommendation for the future, to account for a complementary system of cosmic cycles in and around us. This ever-present transdisciplinary spectrum will have to be considered in focus upon anything singled out as a partial system, as the study of time structure in living matter (chronobiology) investigated in biological data aligned with space and other "weather" series (by chronomics). The invariably present complementary system, a sphere of the mind (noös), Vernadsky's noösphere, undergoes aeolian cosmic cycles mirrored in human affairs, as in living matter broadly, in the chronousphere (Gk chronos, time + Attic Gk nous, mind + Gk sphairos, sphere, globe), the nonstationary glocal (global and local) diversity in space and time of the universe which happens to be our home. This sketch, originally written for a meeting on the history of chronobiology, is here extended in response to a request by Dr. Botond Buda for Folia Anthropologica.

We qualify Pierre Charron (1541-1603), who wrote that "The true science and true study of man is man" (Traité de la Sagesse: Preface du premier Livre), and Alexander Pope (1688-1744), who wrote "The proper study of Mankind is Man" (An Essay on Man, Epistle II), adding, of course, the need for the backtracking of human periodicities over an archaeon to the cosmos (91, 147).

From chronobiology to a unified science

Living matter is variable in time and space, as is weather. The more constant we try to make our proximal environment, the better we recognize seemingly spontaneous variability that reflects the changes around us, near and far. I describe a journey that started with counts of circulating blood cells and action potentials of our brain and the then-surprising periodicities even in RNA and DNA formation and led to the recognition of the drastic importance of timing, among very many other stimuli, exposure to noise first (and x-irradiation and drugs afterward) in the 1950s. What I had then dubbed "circadian stage" made the difference between ~70 or 80% death and ~70 or 80% survival from the same drug, ouabain, or an adrenocortical inhibitor, respectively, or other stimulus. Eventually, I learned that extracircadian rhythms also needed to be mapped; infradians can determine whether we die suddenly because of cardiac malfunction, by our own hand or by that of others. The cycles of the cosmos are found transdisciplinarily and are a challenge as we try to account for them beyond the molecule, at the atomic and quantum levels, with respect to the ever-present associations with space weather.

A perspective in space gains from new complementary imaging tools, chronobiology and chronomics leading (this is humanity's challenge) to chronobioethics. In having fun toward that goal, we can use a set of linear-nonlinear cosinor methods that, whenever possible, should be applied glocally in time and space conceptually and methodologically: nonstationarities are found not only in geo- (and cosmo-)graphy, but also in time, in each case requiring the analyses of the longest available time series as a whole (globally) and in sections varied systematically in length (locally). The resulting atlas, when completed, will, we trust, serve a unified science, providing new preventive and therapeutic marker endpoints for variability anomalies among which coexisting multiple circadian and multiple about 7-day cycles are already mapped and await application for strain relief during wellness. We resonate with the solar flares' about 5-month and the solar wind speed's over 1-year-long periods, as well as with decadals, didecadals, paratridecadals and transsemicentennials of space weather. These contribute to more than blackouts in and around us, including war and terrorism. The study of space weather is thus relevant to human affairs, including an effect on our mood, long anticipated by Alexander Leonidovich Chizhevsky and indirectly documented by Joseph Vallot, validated herein in "the language of shared frequencies" and by remove-and-replace approaches whose application has just begun.

Variability: foe in 1948–49, friend thereafter

Late in 1948, when I arrived at the Peter Bent Brigham Hospital of the Harvard Medical School in Boston, word was that the adrenocortical hormone cortisone, isolated by Edward C. Kendall of the Mayo Clinic (manufactured by the Merck Co.'s Lewis H. Sarett, the likely source of information) given by Philip S. Hench to patients with severe rheumatoid arthritis (1–3), had reproduced the effect of Lourdes: figuratively speaking, patients who came in wheelchairs left walking. This was more impressive than William Withering's (1749-1794) garden. Here, patients with congestive heart failure were said to have brought their ascites in wheelbarrows, which they presumably left after receiving Digitalis purpurea (4). Cortisone was then scarce and a substitute with similar activity was highly desirable. Hence, at Harvard I was assigned to test different substances for cortisone-like activity. Variability was great, so that occasionally the count was spontaneously zero in one or at most two consecutive samples. *Figure 10-I* was on a different stock of mice, but shows the great dispersion of counts (cf. also *Figure 9*). I was given a few mice for testing. One solution, with tests on one or a few mice, was to make sure to bring the count to zero for 24 hours (h), something I did not find occurring spontaneously; I used a large dose of 2.8 mg of cortisone, the truck on the right of *Figure 1* (5) as a reference standard for eosinopenic activity, then a cautious, but wasteful approach, warranted only in view of great variability in count and the limited numbers of mice available for testing and also because the reference standard was scarce. The dose response curve on the left and in the middle of *Figure 1* shows that 1 μg of cortisone was effective in

inducing a relative eosinopenia in the ascending stage of the circadian rhythm in eosinophil count in the mice investigated (when a spontaneous decrease in count was most unlikely to occur).

Epinephrine test of adrenocortical function?

Others in the department of medicine at the Peter Bent Brigham Hospital tested human adrenocortical function: Recant, Hume, Forsham and Thorn (6-8) had postulated, in keeping with C.N.H. Long (9), that epinephrine (from the adrenal medulla) acts upon the hypothalamus, which in turn, via corticotropin-releasing factor, stimulates the pituitary (7, 8) to produce adrenocorticotropin (ACTH), which stimulates the adrenal cortex to secrete corticosteroid which in turn suppresses circulating eosinophil counts. Accordingly a test was recommended for the clinic based on epinephrine-induced eosinopenia, thought to depend upon the presence of the adrenal cortex and which would not occur as a ≥50% fall in the absence of cortical adrenal tissue. It seemed somewhat surprising that epinephrine from the adrenal medulla would have to act via the hypothalamus and the pituitary to stimulate its next-door neighbor the adrenal cortex. Hence, I tested the effect of epinephrine in adrenalectomized and gonadectomized mice with ectopic cortical tissue removed, as best I could, along both sides of the spinal column, in the large ligaments of females and the scrotal fat of males. The eosinophil count decreased after my epinephrine injections by ≥50% when I happened to test. I found eosinopenia in response to epinephrine in mice without adrenals. I reported my inability to confirm the basis of the epinephrine test in mice, presumably deprived of all adrenal cortical tissue (for epinephrine to act upon), to my department head, the late George W. Thorn, Hersey Professor of Medicine at Harvard. Thorn admired my "sticking to my guns", as he put it, but added that all his staff members and distinguished fellows could not be wrong. In the case of the epinephrine test, however, his staff at the time was hardly right (10): in 1952, William R. Best et al. reported on the "clinical and statistical analyses of 702 4-hour eosinophil response tests to corticotropin, ephedrine, epinephrine and placebos in 284 normal and miscellaneous medical subjects", and concluded that "Greater than 50% drop of eosinophils has been noted following epinephrine or ephedrine in patients with pituitary tumors and in patients adrenalectomized and receiving small doses of cortisone. … Tests with these substances are therefore of little value in the diagnosis of adrenal, hypothalamic, or pituitary disease, and do not accurately assess the functional capacity of these organs at the time of examination."

Vascular variability disorders, VVDs

Self- (and others) harming and wrong, by 2012, are those very many (if not all) who still treat variability as a foe or ignore it. Typical is a former head of cardiology at the University of Minnesota who was given a week's half-hourly around-the-clock data on one of his patients. He certainly "honestly" (sic) added that he would gladly check the results (on a variability disorder, with his *single* measurement!). He is not alone. A family practice department head who monitored himself for a week, in whom we found altered variability, went to his care provider in Rochester, Minnesota, and we never saw him again. These instances are the rule. A respected friend, a former cardiology department head at the Mayo Clinic, who monitored himself repeatedly for the senior author's sake only, as he put it, could not be convinced of the merit of monitoring, even when his own data showed that it was helpful (11).

It took more than a generation for the profession to accept the use of the blood pressure cuff at home (not yet to remove it from the care provider's office), a very great progress, re-advocated in the 1970s (12, 13) and implemented in the third millennium AD (14)[3]. It may take another generation to develop a

[3] Self-measurements enabled even the detection of the after-effect upon blood pressure of an earthquake (14). They did not suffice to detect the same event's antecedents and certainly miss all changes occurring during sleep. Automatic records during sleep can provide essential information.

Chronobiologically interpreted Ambulatory Blood Pressure and heart rate Monitoring (C-ABPM) system, *Figures 2A–2F* (15), which may allow even the mapping of infradian, e.g., paratridecadal cycles (16), *Figure 3*, and perhaps some new information thereby concerning the health not only of individuals but also of societies, *Figure 4* (17) and may even detect the antecedents of earthquakes, *Figure 5* (18). If we can have sensors in the tires of our cars and computer chips that continuously monitor pressure over the life of the tire, we should be able to measure, as-one-goes, all rhythms that can form the basis of diagnostic and therapeutic measures. When known or assessed, such rhythms resolve effects of aging and are particularly indicated in view of the epidemic of noncommunicable diseases, referred to as a "slow-motion disaster" (19; cf. 20).

In this context, an immediate reward can be anticipated and has been obtained on a small but worldwide scale by recognizing, for instance, Vascular Variability Anomalies (VVAs) by the cosinor method, *Figures 2A–2G* (21; cf. 12, 22, 23). When these VVAs, *Figure 2D* (15), persist in several automatic 7-day around-the-clock records and become Vascular Variability Disorders (VVDs) (15), treatment is indicated and is sometimes as simple as changing the schedule of hypotensive medication, *Figure 2E* bottom left (24). We try not to repeat the mistakes of the past, such as the failure to scrub before surgery. Measuring and interpreting chronobiologically blood pressure series may seem cumbersome, like scrubbing for antisepsis. Nonetheless, in a computer era, self-surveillance could soon be implemented by everyone, monitoring continuously and affordably. VVAs would gauge loads and teach us how to avoid VVDs as a feature of universal preventive health care. The merit of work with vs. without rhythms is apparent quantitatively in *Figure 1*, showing the dose reduction for corticosteroid-induced eosinopenia by an order of magnitude (from 2.8 mg to one or a few µg [5 vs. 25]).

Qualitatively opposite results obtained in the case of differences in circadian phase, started chronobiology in Minnesota, *Figures 6A* and *6B*, to where the physiologist Maurice B. Visscher (whom I, as an assistant to the dean, had met in Innsbruck before coming to the US, while he was lecturing as a member of a Unitarian medical mission), offered me a chance to move in 1949. Visscher also gave me the task to study adrenocortical function indirectly by eosinophil counts in two groups of mice, with a high and low breast cancer rate, respectively. I compared their counts without realizing at first that they were under the influence of different synchronizers, light for a fully-fed group (feeding in the daily dark span, as rodents do when food is freely available) and the meal time for a group on a calorie-restricted diet (26, cf. 27), *Figure 6*, that happened to be given in the morning and, since limited in calories (from carbohydrate and fat only), was promptly consumed. These initially startling opposite results led us, by the early 1950s, to find the synchronization of a circadian rhythm by timing a calorie-restricted diet when the restriction was by 50%, yet did not involve any changes in the intake of protein and vitamins and thus to find its dominance over the synchronization with that by the lighting regimen, found by us earlier (28).[4]

This was the reason for an intergroup difference in circadian acrophase. Its major generalizable result was methodological; it illustrated the possibility of false intergroup differences in spotchecks that resulted largely from an intergroup difference in phase of the very many variables that exhibit circadian and many

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The blood pressure cuff in the care provider's (physician or nurse) office is no substitute for, and no check of, chronobiologically analyzed serial measurements. The cuff has a place only in the homes of each individual. In the 1960s and 1970s it was worthwhile to plead (12), as Frederic C. Bartter, of Bartter's syndrome, also did, for moving the BP cuff from the providers' offices to everybody's (including his own) workplace by day and taking it home by night. This recommendation holds only until a system of C-ABPM becomes affordably available to everybody, as it is now via BIOCOS. As head of the Hypertension-Endocrine Branch at the U.S. National Institutes of Health (NIH), and later as head of the NIH's Clinical Center, Bartter advocated the need for serial measurements before a physical examination since he, like his predecessors, recognized the unreliability of the best single measurement in individuals who need multiple measurements because of variable blood pressure.

[4] The temporal placement of the 24-hour rhythm in eosinophil count of mice on a regimen of light (L) alternating every 12 hours with darkness (D) can be shifted by offering a diet restricted in calories at the beginning of the daily L-span (28).

other rhythms. The difference in circadian amplitude revealed the real intergroup difference that spotchecks could not detect and thus led to the also generalizable inference that the characteristics of rhythms (cf. *Figure 6*) are the endpoints that must replace spotchecks. Similarly, differences in circadian timing can play havoc with aging research (29), as well as with cancer research (30) restricted to sampling daily at a fixed clock-hour rather than assessing rhythm characteristics. The evidence in *Figure 6* was my first hint that a medical science based on time- and rhythm-unqualified spotchecks as a whole must eventually be replaced by one based on time series for continuous surveillance, a view validated by the ubiquity of circadian rhythms (26, 31; cf. 32).

By 1953, we also learned that the circadian pattern of convulsions (recorded for prior decades in the same patient!), *Figure 7* (left), could be shifted in humans (33, 34) by a change in the timing of sleep and wakefulness, *Figure 7* (right), a finding for which we subsequently encountered an animal model (35, 36) which revealed an increase in vulnerability during phase-shifting (36), *Figure 8* (top left), perhaps because we could also show that different variables shifted at different speeds and hence were transiently desynchronized among each other (36–40).

"Norms", no substitute for concomitant controls: the adrenal cycle, loads, baselines and spotchecks

By the late 1940s, diurnal variation was well-documented (41), yet in studies other than those focusing on rhythms, it was largely ignored, as it is today. The concept of stress was much discussed from the viewpoint of Hans Selye's discovery that many loads, including toxic influences, involved the adrenal cortex (42). Although an inverse relation had been considered between the adrenal and the eosinophil count by Emil Schwarz (43)[5], interest in these cells in North America was triggered by Albert J. Dalton and Selye, who reported an "alarm reaction" based on changes in eosinophils from a "norm", e.g., at 0.5, 1, 2, 4, 6 and 8 h and then again at 24, 30, 48 and 72 h after a treatment, a schedule ignoring any spontaneous changes, yet compatible with a good night's sleep (44). The starting value was the single reference count, the "Norm", irrespective of time of day, and was to serve (presumably as a "baseline") in lieu of concomitant untreated controls.

Dalton and Selye summarize their studies: "It appears that the so-called unspecific leukocytosis preceded by a decrease and followed by an increase in eosinophils, is a constant feature of the alarm reaction" (what they proposed as a result of their investigation was not separated from an ever-present, spontaneously rhythmic feature of everyday physiology before it could be dubbed a special "alarm"). They postulated a "response" to the agent they happened to test, without consideration of variation in eosinophil counts along the 24-hour scale, well-documented in humans (45). By their time (1939), a 24-h rhythm had not yet been described in rodents; a modification of the solution for staining these cells in a counting chamber was needed (46). Dalton and Selye were seemingly unaware of the hardly negligible change as a function of time, subsequently documented by sampling on separate groups of inbred mice, each sampled only once (47), to avoid the "stress" of repeated sampling (48). Such sampling at two clock-hours, *Figure 9* (47), was followed more densely thereafter, *Figure 10* (49).

[5] Schwarz broadly views the autonomic nervous system as the "apparatus leading to eosinophilia". Thus, an increase in autonomic tone by direct stimulation (by pilocarpin) or the loss of inhibition of the sympathetic nervous system led to eosinophilia and vice versa, sympathetic stimulation or the loss of autonomic inhibition (atropin) lower the curve of the count of eosinophil cells. In carrying this thesis to the clinic, the lack of adrenal and thyroidal function leads to eosinophilia and hypertrophy of the chromatin apparatus and of the thyroid to eosinopenia; hence eosinophilia is found in Addison's disease and in myxedema and eosinopenia in Basedow's (Graves') thyroidal hyperfunction. The 2,758 references he discussed, however, are contradictory, often based upon a percentage of eosinophil cells in a smear rather than upon a direct count in a chamber. The changes of eosinophils along the 24-hour scale were not yet known when Schwarz wrote his 652-page opus, nor were the hormones of the adrenal cortex. The isolation of adrenal cortical hormones by Tadeus Reichstein, Edward A. Kendall and Philip S. Hench (for which they received the Nobel Prize in Physiology or Medicine in 1950) postdated Dalton and Selye's paper (44).

The variability of eosinophil counts in mouse strains was particularly great, but hardly the exception (49). Systematic studies at 4-hour intervals on separate groups of animals at each timepoint, were originally carried out to avoid the load (stress) of repeated handling, not only for venisections but also for sampling ear pinna, a point appreciated by Jürgen Aschoff: "Halberg's investigations are so important because they are some of the very few experiments available at this time on the endocrine control of 24-hour periodicity ... that consider to a sufficient extent the possible effects of disturbance and have led for the first time to clear results" (50, 51)[6]. I also learned that this 6/day equidistant sampling scheme, which I introduced, was satisfactory for the fit of a 24-hour period to assess rhythm parameters analyzed in a series of complementary methodologic developments from the population-mean (21) over the single (12) cosinor and the linear-nonlinear cosinor spectrum to a glocal approach in space and time with gliding spectra and serial sections (22, 23; cf. 16, 52).[7] Four-hourly sampling also became routine when the animals had to be killed to remove organs of interest. It often allowed the unaided eye to guesstimate by inspection what curve-fitting tries to approximate with uncertainties whose estimation admittedly remain to be improved, because non-stationarities must be taken into account.

Telemetry

It was cumbersome to work around the clock for days or even years (in the case of the 4-hourly around-the-clock rectal temperature measurements in mice that led to the finding of shorter-than-24-hour periods, dubbed by Earl Bakken as "free-running" (53). We introduced telemetry (54) at least for some variables like body core temperature and eventually kept groups of rats on 6 different schedules of light and darkness, alternating at 12-h intervals, staggered by 4 h, so that freely-feeding rodents could be sampled at six different circadian stages, at a single clock-hour, *Figure 11* (55).

Off and on, I returned to the study of stress and strain and the adrenal cortex on the one hand and to methodology on the other, notably after we found susceptibility rhythms first along the 24-hour scale (*Figure 8*) (35, 36) and then along the scale of a week, *Figures 12A* (56) and *12B* (57). At a meeting at the submarine base in New London, Connecticut (58), Selye indicated to Henri Laborit that the demonstration that circadian stage made the difference between life and death in response to the same stimulus (35, 36; cf. 26), *Figure 8* (top left), was an important finding in the history of medicine. I was the more interested to credit his genius of discovering, documenting and communicating the involvement of the adrenal cortex in the response to stimuli and found particularly drastic changes as a function of injection time after the injection of certain doses of an adrenal cortical inhibitor, SU-4885, *Figure 13A*: the overall difference was

[6] Aschoff's remark (50) reveals that by 1954 (51) others had recognized the need for controls in the study of time-structured variables, apart from the importance of rhythms in themselves, a topic to which Aschoff contributed throughout his lifetime, substantially along naturalistic lines. His comment bears directly upon studies using an initial time-unspecified value as the norm (44), the flaw of very much research then as in 2012.

[7] The development of methodology, a major concern, had a vast field of time series analyses to build on, explored not only by statisticians and mathematicians but also by physicists, among others, including Germaine Cornélissen, whose thesis on the topic prepared her for many subsequent developments. Periodograms and variance (power) spectra were in the forefront in the 1950s and 1960s; we used the former on desk computers and the latter on electronic computers. In view of the nature of the short serial data encountered in the clinic, with replications of a cycle of a given individual sought in others, the population-mean cosinor was developed first (21). The single cosinor followed (12) and, thanks to invaluable help from the late Donald Marquardt, was nonlinearly extended (52). The gliding spectral window by least-squares, developed by George S. Katinas, remains invaluable and reveals what may be smeared by a wavelet, but the latter may also reveal what was missed by a linear-nonlinear cosinor. The chronobiologic serial section was also introduced earlier, as soon as longitudinal data covering many cycles became available in larger numbers to complement the analysis of a long series as a whole by those of its sections systematically varied in length. The need for glocality in time was thus recognized early. The glocal approach is illustrated in (16).

between >80% healthy survivors vs. ~80% deaths as a function of timing (59), impressive and more than matching the findings we made earlier on susceptibility to ouabain, *Figure 13B*, involving the difference, as a function only of circadian stage, in one experiment between ~70% survivors vs. ~70% deaths from the same dose (cf. 60-63). Because of such differences, in the 1960s and for several decades thereafter, the word "stress" was not to be used in my lab when rhythms were not controlled as in the Dalton and Selye report (44). I trust Selye would be pleased if he could see the infradian charts (*Figures 26–30*) that now complement the circadians and render at least some vascular and psychophysiological aspects of stress and strain measurable: alterations of novel rhythm parameters gauge the risks of disease in Osler's wear and tear or Selye's conceptual general adaptation syndrome that required the mapping of spontaneous dynamics (cf. 45).

"Circadian" and "free-running" >60 years later

"Circadian" and "free-running" were coined in 1950; they were only in internal use until 1959 (64; cf. 26), since to start with they were rejected by nomenclature committees. These terms were intended to indicate both the variability and the partly built-in nature of daily rhythms insofar as the periods of inbred mice differed not only from 24.0 h, but some also differed among individuals, *Figure 14-I-C* (Eigenfrequenz) (53). Endogenicity in organisms, always partial in open systems, was based on a) differences in the extent of day/night variation of eosinophil blood cell counts among inbred strains of mice, *Figure 9*, when they had eyes, and b) when eyes were removed (by surgery if not genetics), *Figure 14-IC*, periods (τ) (documented by periodograms by 1954 [65], in the desk computer era) in body core temperature invariably slightly shorter than 24 h, so that the temporal location of within-day differences scanned the 24-h scale.

In 2012, for the purpose of seeking coexisting neighboring circadian τs, we have learned in indispensable months- or years-long around-the-clock data that a circadian free-running can be but one of coexisting (multiple) circadian periods, including socidian 24.0-h periods, wrangling with the ~24.8-h or other components of earth tides in one variable, sleep-wakefulness in health, *Table 1* (66), or in several (including vascular and endocrine) variables under certain conditions in a disease of 21 years standing, *Table 2* and *Figures 15A-15M* on JF (67). In this case, focus on the adrenal cortex is prompted by the adynamia, a symptom of Addison's disease. Focus on the selenosensitivity claimed by JF is in keeping with the double tidal 24.8-h period in the analyses in a computer output (not in the input), not encountered previously in several variables of the same person. The possibility of a beat with cortisol of vigor must be considered as a mechanism underlying JF's adynamia, as visualized in *Figures 15N–15P*.

Back to my first encounter with the adrenocortical cycle

At only one time in history, the earliest 1950s, could adrenalectomy be carried out on patients (68; cf. 10, 69), in the wake of the euphoria from cortisone making lame people walk again (1–3). Thus, a remove-and-replace approach taught us (*Figure 16*) that the 24-h rhythm in serum iron was altered but persisted (34) (ACI: adrenocortical insufficiency) while the rhythm in circulating blood eosinophil counts (68) (and in phospholipid labeling and cell division of adrenalectomized mice; 34) seemed to be eliminated or altered by removing the adrenal (in a 2-timepoint approach) (68). Kaine et al. (69) found that a periodic administration of corticosteroid re-induced the rhythm in humans without adrenals.

Life or death from the same stimulus, including drugs: chronotherapy

Circadian susceptibility rhythms accounting for the difference between survival and death from the same stimulus, e.g., bell ringing, by 1955 (35, 36), and then X-irradiation in mice (70) and a long series of drugs, *Figures 8, 12B* and *13A* and *13B*, became the basis of chronotherapy. By 1977, with B.D. Gupta

and Akhil Deka, the 2-year disease-free survival rate of patients with perioral cancers (receiving radiation treatment at the time of their peak tumor temperature could be doubled, *Figures 17A* and *17B* (71–73). Susceptibility underwent rhythmicity along both the 24-h and the 7-day (circaseptan) scale in vivo, *Figure 12B*, and in vitro (*Figure 18*), in the hands of Waldemar Ulmer, who accounted for the circaseptan cycle at the atomic (74) and quantum (75) as well as macroscopic levels, the latter on the right of *Figure 18*, while therapeutic benefit from treating at maximal β-ATP used as a marker is seen in the middle of this figure (in vitro).

Table 1: On a self-selected schedule (JFC), a double tidal pull competes with 24-hour environment while initially coexisting free-running circadian fades (global analysis)

	Calendar date		**PERIOD**	**AMPLITUDE**	**DT-A/S-A (%)**	
	All (3yr) data	Double tidal (DT)	24.836 (24.833,24.838)	0.10606 (0.0854,0.1268)		**G**
	1990/02/19	Compromise	24.432 (24.427,24.436)	0.05643 (0.0357,0.0772)		**L**
	to 1993/03/11	Free-running	24.260 (24.252,24.268)	0.03253 (0.0118,0.0533)		**O**
		Societal (S)	24.001 (24.000,24.001)	0.25443 (0.2337,0.2751)	**0.41685**	**B**
		Tidal	12.414 (12.410,12.418)	0.01728 (-0.0034,0.038)		**A**
		Semidian	11.999 (11.997,12.001)	0.03204 (0.0113,0.0527)		**L**
•	1: 1990/02/19	Double tidal	24.872 (24.830,24.914)	0.02513 (-0.0070,0.0573)		
•	to 1991/04/28	Compromise	24.409 (24.384,24.435)	0.04117 (0.0089,0.0734)		
•		Free-running	24.222 (24.210,24.235)	0.07921 (0.0468,0.1116)		
•		Societal	24.008 (24.004,24.011)	0.31605 (0.2838,0.3483)	**0.07951**	
•		Tidal	12.421 (12.411,12.431)	0.02615 (-0.0059,0.0582)		
•		Semidian	12.007 (12.001,12.013)	0.04105 (0.0090,0.0731)		
•	2: 1991/04/28	Double tidal	24.898 (24.832,24.964)	0.12744 (0.0707,0.1842)		
•	to 1991/09/23	Compromise	24.707 (24.671,24.743)	0.25208 (0.1973,0.3068)		
•		Compromise	24.488 (24.434,24.541)	0.10274 (0.0552,0.1502)		
•		Societal	24.011 (23.992,24.030)	0.22758 (0.1815,0.2736)	**0.55998**	
•		Tidal	did not converge	—		
•		Semidian	—	—		
•	3: 1991/09/23	Double tidal	24.862 (24.852,24.872)	0.34858 (0.3089,0.3882)		
L	to 1992/03/08	Compromise	24.523 (24.468,24.579)	0.06108 (0.0212,0.1009)		
O		Free-running	did not converge	—		
C		Societal	23.997 (23.984,24.011)	0.22362 (0.1841,0.2631)	**1.55881**	
A		Tidal	12.432 (12.416,12.448)	0.04969 (0.0106,0.0888)		
L		Semidian	did not converge	—		
•	4: 1992/03/08	Double tidal	24.942 (24.896,24.989)	0.15133 (0.0960,0.2067)		
•	to 1992/07/14	Compromise	24.451 (24.394,24.508)	0.11847 (0.0630,0.1739)		
•		Free-running	—	—		
•		Societal	23.987 (23.967,24.006)	0.32099 (0.2660,0.3760)	**0.47145**	
•		Tidal	12.432 (12.398,12.465)	0.04960 (-0.0051,0.1042)		
•		Semidian	11.982 (11.951,12.012)	0.05028 (-0.0044,0.1049)		
•	5: 1992/07/14	Double tidal	24.789 (24.782,24.797)	0.31836 (0.2798,0.3569)		
•	to 1993/03/11	Compromise	24.474 (24.438,24.510)	0.06218 (0.0236,0.1008)		
•		Free-running	—	—		
•		Societal	24.009 (23.997,24.022)	0.17892 (0.1405,0.2173)	**1.77934**	
•		Tidal	12.352 (12.328,12.376)	0.02358 (-0.0147,0.0619)		
•		Semidian	12.001 (11.988,12.013)	0.04128 (0.0030,0.0796)		

The entire available data span was analyzed as a whole (top 6 rows) and then divided into five subspans according to visual inspection of characteristics of 24-hour and 24.84-hour fits in serial sections, suggesting similarities within the spans and differences among them. Initial period (τ) guesses for the six nonlinearly searched τs were 24.84, 24.43,

24.26, 24.00, 12.42 and 12.00. Results were omitted if they did not converge to a τ fitted to the data, in which case the analysis was redone after removal of these components from the model, to yield results summarized herein. Some τs converged well but the CI (95% conservative confidence interval) of the amplitude, A (the CI given in parentheses), covered zero, as apparent from a negative sign inside the last column's second, fifth and sixth sections, for the case of double tidal and tidal associations in the second section (top) where the societal 24-hour day predominates. The double tidal component converges invariably thereafter. Note that overlaps of zero by the CI of the A are very small. In 2 of 5 sections the double tidal cycle has the largest A, the ratio of amplitudes of DT over S becomes greater than 1, suggesting that the moon/sun dominate over society in clinical health. These sections are not consecutive, possibly a chance observation, yet in keeping with the possibility that in health there is a wrangling between the double tide and society, as also seen in a patient with twice-yearly depression. From (66).

Table 2: Recorded recurrent adynamia
Start-end dates and length (weeks) of spans of adynamia when recorded in winter (W) and summer (S).
f: date of full moon; n: date of new moon

	2002	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**
W	-	01.18 f 02.17 f (4)	01.12 02.20 n (5)	01.05 02.15 (5)	12.25 n 02.14 n (7)	01.03 f 03.03 f (8)	01.08 n 02.21 f (6)	12.26 n 02.23 n (8)	01.02 f 02.28 f (8)	01.04 n 03.05 n (8)	01.04 -**
S	06.09 08.07 (8)	06.15 f 08.12 f (8)	06.17 n 08.18 n (8)	06.20 f 08.09 (7)	06.04 08.28 (11)	05.31 f 08.12 n (10)	? 08.18 f (?)	06.09 f 08.08 f (8)	07.08 09.16 (10)	07.07 09.13* (10)	

*"I have concluded that Sept 1 was a false end to the downtime. I had five functional days, but the last eight [i.e., 09.06-09.13] have been horrible again!" (JF, personal communication, 14 September 2011)
**"Although there have been many failed attempts to regain a normal sleep schedule (which has in the past been a clearly noted evidence that the downtime is over), I have not been able to do so" (JF, personal communication, 15 April 2012)

Cellular timing

By 1958, a combination of methods, including radioactive tracers, differential centrifugation and wet chemistry, enabled the demonstration of circadian rhythms in the formation of RNA and DNA (76), with RNA synthesis preceding that of DNA, *Figure 10*, and growth hormone acting in just one stage of this first mapped circadian cell cycle (77, 78). In 1960, this cell cycle (of *Figure 10*) was reported and depicted as a basic complement to the hypothalamus, *Figure 19* (70; cf. 40), as accepted today but denied at the time and for several decades thereafter. Thus, against the prevailing bias of the vast majority of a Naito meeting published in 1979 (79), it was re-emphasized that circadian timing resides in peripheral cells as well as in the suprachiasmatic nuclei (SCN) of the hypothalamus (80, 81). Unless the data were interpreted by visual inspection alone (26, 82, 83), SCN removal (as in the case of adrenal removal) eliminated some rhythms (in motor activity and water drinking) but not those in core temperature, alcohol drinking, corneal mitosis or thymidine labeling in the gastrointestinal tract, *Figures 20A* and *20B*. A report on the loss of the circadian rhythm in core temperature was revised when the data were reanalyzed (82 vs. 83). An amplification of thymidine labeling was found in the stomach after bilateral SCN ablation, *Figure 20B*, and in core temperature after unilateral ablation, *Figure 20A* (lower row), the latter finding interpreted as subtractive coupling between the two nuclei (80; cf. 26, 49).

Along a different line of thought, removal of the SCN suggests its mediation of earth tidal effects by the loss of the 24.8-hour (double tidal) period in core temperature of rats kept in continuous light of low intensity (49), *Figure 20A-III*. This 24.8-hour component was also found in the self-selected sleep pattern of a healthy man during 3 years, *Table 1* (66), and in the longest (>260-day) human isolation in a cave study (84, 85), *Figure 21*, among many other, shorter but important studies of human isolation in shielded and unshielded bunkers by Ruetger Wever (86). He recorded periods that could have been interpreted, as we did for one of them we analyzed, as close to 24.8 hours.

Prokaryotes

By 1961, a circadian cycle shorter than 24 hours (of ~21 hours) was found in growth or colony advance of a prokaryote (87), *Figures 22A-22D*, and extended in scope (88), but was ignored for subsequent decades by those "naturalists" for whom periodograms and power spectra were (in the words of a personal communication by a sympathetic committee member) "too much mathematics". Not realizing that ruling out a rhythm is difficult with the unaided eye (it requires time series analysis), a committee erroneously decreed, and its decision was accepted by many others for many years, that circadians were limited to eukaryotes (89) until eventually a flood of papers on rhythms in prokaryotes set the record straight (90). In 2010, we learned about a rhythm in an archaeon, *Figure 23* (91).

Eukaryotes

In eukaryotes, the circadian cycle could be tracked from the adrenal to the cell, the pituitary and the hypothalamus by 1959 (40) and eventually to the suprachiasmatic nuclei and the pineal (55), resulting in rhythms of different orders (cf. *Figure 14*) explored with novel designs (*Figure 11*) leading to feedsideward interactions, replacing, whenever feasible, or complementing time-unqualified feedbacks and feedforwards (92).

Infradians: chronomics

Free-running repeated itself for the biological week, *Figure 24*, which in turn led to its physical counterpart in geomagnetics, *Figure 25A* (93; cf. 94, 95) (as well as to an earlier reported week in rainfall, *Figure 25B*), starting chronomics with the postulate that for each biological cycle there should be an environmental cycle with a similar period, τ (in the sense of overlapping CIs, 95% confidence intervals, of their τ), and vice versa (96). A unique set of self-ratings and self-measurements for over 40 years of Robert B. Sothern (97), and shorter records of others, allowed the demonstration of paratridecadal Brückner-Egeson-Lockyer (BEL) cycles with a CI of τ near or in the about 30-40-year range (16), *Figure 3B*. A BEL cycle in environmental temperature could be a first harmonic of the about 60-year climate temperature cycle (16), described by Enfield and Trimble as a 65-80-year cycle with an 0.4˚C range (98) while Schlesinger and Ramankutty report for 11 geographic regions that "the 65-70-year oscillation is the statistical result of 50-80-year oscillations for the North Atlantic Ocean and the broader Northern Hemispheric continents" (99; cf. 100). It is the more interesting to find these periods in neonatal anthropometry, in the length, weight and head circumference at birth of the human neonate (101), *Table 3*, a sensitive magneto- and broader cosmo-meter (102, 103), showing ~50- and ~60-year cycles and one ~80-year cycle, all congruent with the global multidecadal temperature cycle as trans-semicentennians.

These decadal, didecadal and paratridecadal cycles in longitudinal records of ~6 daily self-measurements (by now for well over 4 decades) (97; cf. 104) were later complemented by automatically collected around-the-clock half-hourly and decades-long blood pressures and heart rates with gaps (105). Like the manually recorded self-surveillances, the automatic self-surveillances mirrored cycles in space and/or earth weather, *Figures 26-30* (as noted, with their ever-present uncertainties). Moreover, the set of records as a whole suggested a selective assortment of paired periods, coperiodisms, in and around us, that were congruent by virtue of their overlapping CIs (95% confidence intervals). Whether this assortment is a matter of chance cannot be ruled out, yet it seems important to note the fact, in any event, that different variables and even different characteristics such as the circadian MESOR vs. circadian amplitude of the same variable in the same person can show modulations by different environmental periods, whether or not they are related to different aspects of space weather (106). The latter has too many mapped components to draw inferences to direct causal connections from congruence of τs only.

Table 3: Period(s), τ, in years in body length (cm) at birth in Russia 1874–1985: data of Boris Nikityuk*

	Boys (overall standard error: 0.44)	**Girls (overall standard error: 0.47)**
MESOR	52.224 (51.962, 52.687)	51.564 (51.288, 51.840)
Slope	-0.017 (-0.027, -0.008)	-0.015 (-0.025, -0.005)
τ 1	53.671 (46.12, 61.23)	53.666 (42.00, 65.33)
Double amplitude	1.52 (0.74, 2.28)	1.32 (0.42, 2.22)
Acrophase	-276˚ (-247, -305)	-274˚ (-237, -311)
τ 2	32.404 (29.35, 35.13)	33.487 (25.88, 41.09)
Double amplitude	0.76 (-0.00, 1.50) [0.42, 1.08]	0.86 (0.00, 1.74) [0.48, 1.24]
Acrophase	-243˚ (-187, -300)	-207 (-151, -263)
τ 3	20.441 (18.31, 22.57)	21.217 (19.18, 23.25)
Double amplitude	0.84 (0.56, 1.10)	0.94 (0.62, 1.24)
Acrophase	-184˚ (-129, -240)	-158˚ (-109, -208)

*95% confidence limits in ( ) are conservative; in the case of a very slight overlap of zero beyond the second decimal, 1-parameter limits are given in [ ].

Congruent cycles in and around us are noteworthy, but do not validate relations. Whenever possible and the cosmos cooperates, a remove-and-replace approach is indicated where the sun does the subtraction and addition (replacement) of a component in its spectrum and we examine whether the biosphere responds accordingly (104–106). If the physiological cycles are amplified when the environmental counterpart is detected and is increasing, we conclude that we are driven from outside the organism. When the environmental component is no longer detected and the biospheric component dampens in amplitude yet persists, we conclude that it is built into living matter (105). Such environmental behavior, including disappearance of a component, be it because it is transiently lost or just obscured by noise, could actually be documented in several cases (104–106) where, to paraphrase Sir William Herschel (107), the sun (the measurable solar wind's speed or sunspot number or area) was "well-disposed" insofar as it cooperated by the subtraction or addition of a weekly or transyearly component in its spectrum.

Myriadennians with a period of 200 million years (MY) between ice ages (108; cf. 109) come to mind when cycles of the order of 260 MY are found by Rohde and Muller (110) in the extinction of species repeating itself at the bottom of the sea and are complemented by their uncertainties and Cornélissen's cycle of 37.81 MY with a 95% confidence region extending from 36.64 to 38.97 MY (111), which corresponds to a major step in water cooling, revealed by marine sediments (108). τs in MY in species diversity show the width of the spectrum of biospheric cycles, all sought to be paired eventually with environmental ones, dubbed the Cornélissen-series (112) that awaits much more aeolian mapping. Physical cycles that were mapped in us after their discovery around us, and vice versa, namely a near-transyear (1.00 year < [τ - CI] < [τ + CI] < 1.20 years), Figure 31A, in solar magnetism, was found because of biological counterparts (105) (as in the case of the near-week in geomagnetism) (93). By contrast, an ~154-day cycle of solar flares with τs of about 5 months, the quinmensal or cis-half-year was found by physicists, *Table 4*, and thereafter in circulating melatonin (113), *Figure 31B*, in 17-ketosteroid excretion (114), heart rate, *Figure 31C*, and blood pressure (115) , *Figure 31D*. Nonstationary infradian τs in space and time, dubbed aeolian, found in the biosphere also include τs much longer than a year, far-transyears (1.20 years ≤ [τ - CI] < [τ + CI] < 1.90 years) (105; *Figure 32*), the latter extended to natality, epilepsy and stroke incidence by Prof. Miroslav Mikulecky (116–119) and by Mauricio Pacheco de Andrade to a clinical chemical database on uric acid excretion (120).

Table 4: Point estimates of a cis-half-year (~154-day) periodicity, sometimes given with estimates of uncertainty and hypothesis testing

Period (in days except where noted)	**Reference**
154.3	Wolff CL. The rotational spectrum of g-modes in the sun. Astrophys J 1983; 264: 667-676.
154	Rieger A, Share GH, Forrest DJ, Kanbach G, Reppin C, Chupp EL. A 154-day periodicity in the occurrence of hard solar flares? Nature 1984; 312: 623-625.
158	Kiplinger AL, Dennis BR, Orwig LE. Detection of a 158-day periodicity in the solar hard X-ray flare rate. Bull Am Astronom Soc 1984; 16: 891.
152	Bogart RS, Bai T. Confirmation of a 152-day periodicity in the occurrence of solar flares inferred from microwave data. Astrophys J 1985; 299: L51-L55.
152-158	Dennis BR. Solar hard X-ray bursts. Solar Physics 1985; 100: 465-490.
152	Bai T, Sturrock PA. The 152-day periodicity of the solar flare occurrence rate. Nature 1987; 327: 601-604.
near 155	Lean JL, Brueckner GE. Intermediate-term solar periodicities – 100-500 days. Astrophys J 1989; 337: 568-578.
152	Özgüç A, Ataç T. Periodic behavior of solar flare index in solar cycles 20 and 21. Solar Physics 1989; 123: 357-365.
154 (± 0.6)	Bai T, Cliver EW. A 154 day periodicity in the occurrence rate of proton flares. Astrophys J 1990; 363: 299-309.
near 155	Carbonell M, Ballester JL. A short-term periodicity near 155 day in sunspot areas. Astron Astrophys 1990; 238: 377-381.
153	Dröge W, Gibbs K, Grunsfeld JM, Meyer P, Newport BJ, Evenson P, Moses D. A 153 day periodicity in the occurrence of solar flares producing energetic interplanetary electrons. Astrophys J Suppl Ser 1990; 73: 279-283. Applying Rayleigh test for periodicity.
155	Lean J. Evolution of the 155-day periodicity in sunspot areaas during solar cycles 12 to 21. Astrophys J 1990; 363: 718-727.
155	Silverman SM. The 155-day solar period in the sixteenth century and later. Nature 1990; 347: 365-367. "[A]lthough values between 150 and 160 days have been reported, I refer to it here as the 155-day period, for convenience"
154	Bai T, Sturrock PA. The 154-day and related periodicities of solar activity as subharmonics of a fundamental period. Nature 1991; 350: 141-143.
154	Kile JN, Cliver EW. A search for the 154 day periodicity in the occurrence rate of solar flares using Ottawa 2.8 GHz burst data, 1955-1990. Astrophys J 1991; 370: 442-448.
152-158	Verma VK, Joshi JC, Uddin W, Paliwal DC. Search for a 152-158 days periodicity in the occurrence rate of solar flares inferred from spectral data of radio bursts. Astron Astrophys Suppl Ser 1991; 90: 83-87.
154	Bai T. The 77 day periodicity in the flare rate of cycle 22. Astrophys J 1992; 388: L69-L72.
near 155	Carbonell M, Ballester JL. The periodic behaviour of solar activity: the near 155-day periodicity in sunspot areas. Astron Astrophys 1992; 255: 350-362.
152	Verma VK, Joshi JC, Paliwal DC. Study of periodicities of solar nuclear gamma ray flares and sunspots. Solar Physics 1992; 138: 205-208.
154	Bai T, Sturrock PA. Evidence for a fundamental period of the sun and its relation to the 154 day complex of periodicities. Astrophys J 1993; 409: 476-486.
~153	Cane HV, Richardson IG, von Rosenvinge TT. Interplanetary magnetic field periodicity of ~153 days. Geophys Res Lett 1998; 25: 4437-4440.
158	Oliver R, Ballester JL, Baudin F. Emergence of magnetic flux on the Sun as the cause of a 158-day periodicity in sunspot areas. Nature 1998; 394: 552-553 | doi:10.1038/29012
near 158	Ballester JL, Oliver R, Baudin F. Discovery of the near 158 day periodicity in group sunspot numbers during the eighteenth century. Astrophys J 1999; 522: L153-L156.
151-155	Lou YQ. Rossby-type wave-induced periodicities in flare activities and sunspot areas or

Period (in days except where noted)	Reference
	groups during solar maxima. Astrophys J 2000; 540: 1102-1108.
153.9	Hady AA. Analytical studies of solar cycle 23 and its periodicities. Planetary and Space Science 2002; 50: 89-92.
156	Krivova NA, Solanki SK. The 1.3-year and 156-day periodicities in sunspot data: wavelet analysis suggests a common origin. Astron Astrophys 2002; 394: 701-706.
near 160	Ballester JL, Oliver R, Carbonell M. The near 160 day periodicity in the photospheric magnetic flux. Astrophys J 2002; 566: 505-511.
near 5-month	Han Yanben, Han Yonggang. Time variation of the near 5-month period of sunspot numbers. Chinese Sci Bull 2002; 47 (23): 1967-1973. "Many scholars ... found similar periods of solar activity from other observations of the Sun. However, these periods are different, such as about 152-, 154-, 156-day, etc. Here we name it a near 5-month period (N5MP) since it is not definite."
154	Prabhakaran Nayar SR, Radhika VN, Revathy K, Ramadas V. Wavelet analysis of solar, solar wind and geomagnetic parameters. Solar Phys 2002; 208: 359-373. "The global wavelet spectra of these parameters ...exhibit the presence of a variety of prominent quasi periods around 16 years, 10.6 years, 9.6 years, 5.5 years, 1.3 years, 180 days, 154 days ..."
153	Bai T. Periodicities in solar flare occurrence analysis of cycles 19-23. Astrophys J 2003; 591: 406-415.
near 160	Ballester JL, Oliver R, Carbonell M. Return of the near 160 day periodicity in the photospheric magnetic flux during solar cycle 23. Astrophys J 2004; 615: L173-L176.
151-158	Knaack R, Stenflo JO, Berdyugina SV. Evolution and rotation of large-scale photospheric magnetic fields of the Sun during cycles 21-23: Periodicities, north-south asymmetries and r-mode signatures. Astron Astrophys 2005; 438: 1067-1082.
~152	Chowdhury P, Ray PC. Periodicities of solar electron flare occurrence: analysis of cycles 21–23. Mon Not Roy Astronom Soc 2006; 373: 1577-1589.
155	Chowdhury P, Ray PC, Ray S. Periodicity of 155 days in solar electron fluence. Ind J Phys 2008; 82: 95-104.
150-160	Dimitropoulou M, Moussas X, Strintzi D. Enhanced Rieger-type periodicities' detection in X-ray solar flares and statistical validation of Rossby waves' existence. Mon Not R Astron Soc 2008; 386: 2278-2284.
158	Javaraiah J, Ulrich RK, Bertello L, Boyden JE. Search for short-term periodicities in the sun's surface rotation: a revisit. Solar Phys 2009; 257: 61-69.
155	Vaquero JM, Trigo RM, Vazquez M, Gallego MC. 155-day periodicity in solar cycles 3 and 4. New Astronomy 2009. doi: 10.1016/j.newast.2009.11.004
155-160	Zaqarashvili TV, Carbonell M, Oliver R, Ballester JL. Magnetic Rossby waves in the solar tachocline and Rieger-type periodicities. arXiv:0911.4591v1 [astro-ph.SR] 24 Nov 2009
154	Fischbach E, Jenkins JH, Buncher JB, Gruenwald JT, Sturrock PA, Javorsek D II. Evidence for solar influences on nuclear decay rates. arXiv:1007.3318v1 [hep.ph] 20 Jul 2010

This incomplete list (added contributions are cited in the references provided) suffices to indicate the variable nature of the period being discussed. Specifications of the decadal solar (Horrebow-Schwabe) cycle in which they are found point indirectly to the intermittency of the components being discussed.

When to eat

Another Minnesota lesson is that the timing of a meal restricted in calories can make the difference between survival vs. death (121) in laboratory mice (without ample fat reserves; but not in rats), in cool temperature with single housing to prevent cuddling. This study was prompted by our experience in India where, among palm trees in Varanasi, in cool (not cold) temperature, I read a newspaper report on a number of deaths among poorly dressed, undernourished people. We were also surprised to learn on

humans that clinically healthy students on 2000 calories in a single-meal/day experiment on "breakfast-only" lost body weight, while on "dinner-only" they (and other staff members) had a (relative) gain in weight, *Figures 33A-33G* (122).

When to treat

Like timed radiotherapy, chemotherapy guided by salivary marker rhythms also awaits entry into everyday clinical oncotherapy (78; 123–126). Much to-us convincing laboratory investigation, *Figure 34*, in cancer, *Figures 34A-34I* (127), and in hypotensive therapy (128; cf. 129), *Figures 34J-34L*, and clinical evidence based on marker rhythms is not yet utilized in oncology, preventive cardiology, psychiatry, *Figure 15*, and health care generally, *Figure 2*. Timing treatment is also a challenge in other fields, notably in cardiocerebrovascular disease. Immediately applicable cost-effective, urgent and most promising, in view of the slow-motion disaster (19) of non-communicable disease in very many millions of people in developing areas, is a hypotensive treatment that does not fly blind, as it currently does between visits to a care provider (15, 130; cf. 106). Chronobiologic self-surveillance optimally clarifies when stress becomes strain by gauging partly novel vascular variability anomalies, VVAs; disorders, VVDs, and syndromes, VVSs, *Figure 2* (15, 130), providing the means to reach Selye's goal of "stress without distress" (131). That chronobiologically-interpreted ambulatory monitoring detects antecedents of natural disasters such as earthquakes, *Figure 5* (18), for possible evasion, as well as those of personal cataclysms such as strokes is all part and parcel of a unified science and art without disciplinary borders; it starts relating to health care when music therapy rather consistently alleviates all symptoms, at least for a while, in JF, a patient with adynamic depression who was not helped by drugs during her 20-year history of adynamia and still depends on palliatively successful music therapy (132). The same case documents sensitivity to earth tides by the demonstration of a (double tidal) 24.8-hour period in several variables in the computer output of analyses (67), complementing an earlier cosinor demonstration of a tidal effect on cardiac arrhythmia by Miroslav Mikulecky (133).

Encounters

Prof. Dr. (med.) Dr. (theol.) Mag. (pharmacist) Gustav Sauser, whom I met while he practiced as a pharmacist in Wels, Upper Austria, after he lost his professorship during the occupation of Austria in World War II, granted me an opportunity for an academic connection. After the war, he was appointed as the head of the anatomy department at the University of Innsbruck, and in succession became its dean and rector. Sauser offered me a room in his bombed-out anatomy department building; as his assistant, I participated in international academic weeks (134, 135) where I met the physicist Arthur March (a friend of Erwin Schrödinger), with whom I developed an interest in physics. There, I also read Galileo and the statement attributed to him that I (and others including physicists and historians I consulted had cited) could never identify in his writings: "Measure what is measurable and render measurable what as yet is not", which became the guiding principle of my endeavors and to which I added qualifications like "in time and hence meaningfully": "Measure, in a partial system, everything pertinent that is measurable and render measurable what is pertinent but as yet is not measurable, as simply as possible, but not simpler, in time (tempestive) and hence meaningfully, taking into account chronomic maps, a described and quantified complementary system" [Omnia propria ex systemate partiali metire quæcumque licet et propria immensa, quam simplicissime sed non simplicius, ad mensuram tempestive et ergo significative redige, reddens rationem tabulae chronomicae – systematis complementaris, descripti et quantificati].

While in Innsbruck from 1946-1948, I also headed the section of venereology and dermatology at the French military hospital, where I encountered my first case in which timing could possibly have played a role. In two identically treated soldiers who contracted gonorrhea from the same prostitute on consecutive nights, the same treatment begun the same day cleared gonococci first from the patient who was infected a

day later (136). I also owe Sauser my World Health Organization fellowship that brought me to Harvard in 1948.

Opportunities enjoyed and yet to be followed up upon

In Minnesota in 1950, I met Prof. Alan Treloar, who renewed my interest in the inferential statistical validation of all I learned. In 1961 I began receiving a lifetime career award from the U.S. National Institutes of Health (NIH); at >92 years of age, I am still receiving it. I may be one of only two still-active recipients of these awards. A contract to study the endocrine associations of breast cancer, also from the NIH, led to multifrequency models of infradian risk assessment. We found modulations by both about 30-day and about-yearly rhythms of the circadian MESOR and amplitude demonstrating them stepwise as partial spectral structures based on parameters obtained by the least-squares fit of cosine curves of 24 hours and 28 and 365 days to data on plasma prolactin, *Figures 35–38* [8] (137). These are obtained every 20 minutes and other hormones at 100-minute intervals for 24 hours, in 4 seasons on 3 age-groups of Japanese and Minnesotan women, *Figures 35A-35F*, to derive tentative gauges of breast cancer and other disease risks. We then wrote something still pertinent today:

> Once we realize that a spectrum of rhythms exists [*Figures 26–38*] and what its components are, we have a chance to specify how, with very few samples if not with a single sample, at the right time for each pertinent variable, one may [try to] achieve multiple aims. One may quantify certain aspects of health. One may recognize risk – before disease sets in, as a basis for prevention. One may also learn when one should look for what and where in the body – in a study of physiological mechanisms, safeguarding our performance – the neuroendocrine and cellular feedsidewards leading to a yet to be tested hemopsy. (137–140)

The extension of this model of 1981 (137) to include the periods mapped in the interim of 30 years as coperiodisms in and around us, up to paratridecadals, remains a major challenge for marker rhythmometry.

Whenever possible, for disease risk assessment by infradian modulation, we should prefer the noninvasively collected saliva or urine to plasma. A study of 11,702 samples on 6 hormones in saliva collected every 4 hours around the clock for many months, *Figure 15*, reveals new facts, such as not only multiple distinct frequencies in a very broad spectrum, but also, i.a., multiple circadians. Multiple circaseptan frequencies, *Figures 39A* and *39B*, were also found in cases where, under life in contemporary society, we expected to find only a single circadian or circaseptan frequency, which is or is not environmentally synchronized. As noted earlier, there are multiple coexisting circadian frequencies, *Table 1* and *Figure 15*. Thus we arrive at new diagnoses; once we rely on time series, we may quantify even the effects of the earth tides on humans (67, 141). Serial data in turn require glocal methods in time and space, notably if focus is extended beyond the circadian system (104–106).

In the early 1960s, representatives from NASA were the first to knock on my door and ask what they could do for Minnesotan chronobiology. NASA, the National Science Foundation (NSF) and NIH enabled the completion of a laboratory for periodicity analysis, with standardization, if not full control, of environmental temperature and lighting, and as best we could of sound and smell, since they were the candidate factors accounting for the synchronization of the eosinophil count's circadian rhythm in

[8] A much larger circannual amplitude in circulating prolactin of Japanese as compared to American women, based on nearly 3,000 determinations (137), had as a result that in different seasons at different clock-hours, timing can certainly make the difference between finding or not finding a higher prolactin in plasma of Japanese vs. Americans, and numerically the results can even happen to be opposite at different clock-hours in certain seasons (137). Based on fewer samples, a comparison of melatonin excretion by the two populations of women at different clock-hours can also show opposite results.

commonly, but not in singly housed mice without eyes (deprived of them by surgery or genetics, ZRD) (65). NASA also supported the introduction of temperature and other telemetry in preparation for a Biosatellite study that remains a challenge, as does that of a lunar laboratory (142). In extraterrestrial space, away from hospitals, it will be especially important to detect undue strain and to alleviate it, a task also critical on earth.

It cannot be overemphasized that cycles, when not considered, can be confounders, i.a. *Figure 15*, or when two cycles being compared differ in phase, *Figures 6A* and *6B*, or in frequency or for those very many investigators sampling at a single clock-hour with an interest in aging. A human mental function, such as the duration of an estimation of one minute, may decrease with age at one time of day while at another clock-hour in the same person in the same longitudinal time series an increase with age is found, *Figure 40* (29). This is a necessary a priori consequence of a decrease in circadian amplitude (or of a change in phase) with age. If other characteristics do not change (they actually do in the case considered), a decrease with age of the circadian amplitude results in an increase at the trough, and a decrease at the peak of a daily rhythm, as readily visualized by a 24-hour cosine fit at the start and at the end (not shown).

Fortunately, the puzzles of *Figures 6A* and *6B* were solved and nonsensical partial results were not published. Interest in full- and overtime study of the cosmos resulted from our inability to validate a test developed and published by ourselves in Minnesota (143), confirmed abroad for 2 years, yet subject to a modulation by an, initially unknown, circadecadal rhythm, which could eventually be found in the circadian blood pressure amplitude of newborns (103). The challenge remains to test other-than-circadian, e.g., circaseptan amplitudes that may be less confounded by decadal changes for diagnosing the neonatal risk of developing cardiovascular disease later in life, even though an effect of geomagnetism upon them has been demonstrated (144).

Sooner rather than later we must deal with a broad spectrum of non-photic, partly gravitational and/or magnetic novel paired transdisciplinary cycles in and around us in the sphere of the human mind (noös), Vernadsky's noösphere. Mikulecky and Pales' ~500-year cycle (145, 146) in the emergence of prominent poets, historians and physicians, with counterparts in cave temperature and the incidence pattern of international battles (147), *Figures 41A-41E*, show the extent to which the cosmos modulates human affairs, including science and art, leading to a temporally structured chronousphere, coined by portmanteauing the Attic Gk nous (= noos), into Gk chronos (=time) and Gk sphairos (=globe as well as sphere). There is no choice for a unified art and science, whether in the service of health care, anthropology or a unified science, but to monitor from birth to death with repeated passes over the accumulating data so as to determine loads before they become undue strain and harbingers of disease, to start with in blood pressure and heart rate. Monitoring has to start during wellness (15) for the prevention of illness as soon as affordable unobtrusive instrumentation yields data analyzed via an international multilingual website, the recommendation of a World Forum on "Natural Cataclysms and Global Problems of the Modern Civilization", held 19–21 September 2011 in Istanbul, Turkey (www.2011.geocataclysm.org).[9]

[9] A small-scale ongoing chronobiologically interpreted C-ABPM system, serving for cost-free analyses of self-surveillance data by all comers by the project on The BIOsphere and the COSmos, BIOCOS (96), has shown decadal and multidecadal solar periods in the human circulation on the as-yet basic side. From an applied viewpoint, BIOCOS also represents a de facto validation test, on a small scale but worldwide, of C-ABPM. A model for a website has now also been proposed by the World Forum in Istanbul. The data collected for the prevention of personal cataclysms, such as a massive stroke, may also be used to attempt an understanding (for countermeasures) of the mechanisms whereby space weather contributes to societal disease, such as suicide, crime, homicide, terror and war and natural disasters such as earthquakes and tsunamis, a task for which the mapping of the time structures of these phenomena has begun, with results all revealing solar-biospheric coperiodisms.

So what?

That the aeolian sunspots (actually their cycles) affect many aspects of our physiopathology was documented by Vallot et al., whose data are meta-analyzed in *Figure 42*. The proposition that infectious diseases such as cholera may be influenced by the cycle in Wolf numbers is one of Alexander Leonidovich Chizhevsky's many lines of evidence, sometimes aptly based on aeolian original data with solar cycles reporting millions of cases near the peak of one cycle of solar activity, while in another, no cases are recorded. On the average there is a semidecadal (instead of a decadal) cycle (148). With selected superposed epochs, Chizhevsky certainly made the case that infections in humans are influenced by solar activity, even though he only mentioned the spectra produced by his friend Vladimir Boleslavovich Shostakovich, which in the case of cholera in Moscow, in meta-analyses by Lyazzat Gumarova, show that overall (globally), the harmonics of the circaundecennian sunspot cycle were more prominent than the fundamental, which was the one Chizhevsky illustrated as of interest, locally in time: the privilege of genius.

That the same hormone can have opposite effects as a function of circadian cyclicity, *Figure 43*, may be new to some. That the same 2000 calories at breakfast-only can lead to body weight loss vs. body weight gain on dinner-only, *Figure 33*, may be noteworthy. *Figure 19* is welcome, showing the doubling of a 2-year survival rate by cancer chronotherapy timed by tumor temperature, which is just a page of an overdue chrono-oncology based on triangulation guided by marker rhythms (73, 140). But when we deal with figurative cancers of the human mind (i.e., with man's inhumanity to man), we rest the case for a sphere of the human mind to be optimized, i.e., of a chronousphere, a page of anthropology par excellence with a reference to some of the poems of Chizhevsky (1897–1964) (149), who put his thoughts equally memorably (poetically) in prose: "Peut-être même nos sentiments et nos pensées ne sont-ils qu'un faible écho de ces vibrations du cosmos .... Involontairement, une antique idée nous vient à l'esprit: notre connaissance des phénomènes de la nature ne serait pas autre chose qu'un écho, reçu par nos organes, des processus réels de l'univers" ("Perhaps even our feelings and thoughts are just a weak echo of the vibrations of the cosmos .... Involuntarily an old idea comes to mind: Our knowledge of natural phenomena will not be different from an echo, received by our organs, of the real processes of the universe") (149). Actually, the analysis of a near 40-year record of self-measurements and self-ratings supports this poetic aspect of his "cosmism" (150) by objective results in *Figure 44* (151, 152).

An influence on human psychophysiology, poetically anticipated by Chizhevsky (149), of the antipodal index of geomagnetic disturbance aa (*Figure 44*, top) and of the non-photic extraterrestrial environment (gauged by solar wind speed, an approximation of interplanetary magnetism, *Figure 44*, bottom) was assessed by means of the congruence of periods, τ, of spectral components (defined by overlap of the 95% confidence intervals of the τs, in the frequency range of one cycle in 2.5 years to 3 cycles per year). The biological data stem from ~40 years of self-measurements (of oral temperature [Temp], systolic blood pressure [SBP], diastolic blood pressure [DBP] and heart rate [HR] and of ratings of mood and vigor and the estimation of 1-minute by counting [1MTE], performed about 6 times a day by a clinically healthy man, Dr. Robert B. Sothern). Congruences (assessed by means of odds ratios based on the noncentral hypergeometric distribution) found for 1MTE and for other human mental functions more than equal those of the known association of helio- and geo-magnetism (bottom, last column on right of dashed vertical line in blue). Mental functions (full red) show higher congruence than somatic functions (green). Among the latter, systolic blood pressure (SBP) is responsive, perhaps constituting a seemingly acceptable proxy for the mental functions. P-values are based on the non-central Fisher hypergeometric distribution, with 95% confidence intervals computed using Fisher's exact test, used since the null hypothesis was rejected in some, yet not all cases (151, 152). Much more remains to be learned on how the human mind can optimize its terrestrial, cosmically influenced habitat in the same language of frequencies.

Maps

The mapping of circadian rhythms with their uncertainties in several species is illustrated in *Figures 45A-45D*. It was a pleasure to comply with a request to publish one of these charts by an opinion-leading naturalist, Colin Pittendrigh, who included it, with its uncertainties, in his swan song (153). For apparent clarity, it is unfortunately tempting for others to "simplify" such charts by omitting the wide, possibly still liberal 95% confidence intervals. These, however, are indispensable for all mapping in and around us, as in *Figures 45* to *47A-47D*, in a complementary monograph on chronoauxology (154), in an introduction to chronobiology (49) and in the American Journal of Anatomy (31). Infradian mapping must continue on both a population basis and in individuals' circulation, *Figures 26–30*. A map of a much broader psychophysiology by Robert B. Sothern (155, 156), already complements for this individual, in *Figure 48*, by some aspects of infradian temporal coordination, the circadian map shown in *Figure 45*, there only for populations.

Morphology in space and time exhibits multiple coexisting cycles, ranging in length from fractions of seconds to decades in individuals and to still longer periods in populations of living matter, including cycles of 142 [95% CI: 133-150], 62 [60-63] and 38 [37-39] million years in species diversity (111). In populations, these cycles are synchronized among individuals; they can be demonstrated by time series to which each individual organism contributes just a single value. I learned this along the circadian scale from eosinophil counts (47) and from RNA and DNA synthesis (76), in this order, on inbred mice, well over 50 years ago. During the individual human's lifespan, some of the decadal cycles demonstrated in population – across individuals by neonatal anthropometry over 112 years or longer (transverse sampling) (101) – could be reproduced longitudinally in *Figures 26–30* (105, 155-157; cf. 10). Sooner or later physiological monitoring may be from womb-to-tomb with technology already available for mice (to test drugs) and for tires (for security). In the case of tires, the pressure sensor technology was apparently developed in the mid-1980s but was not deployed to commercial applications until 2000, after a poorly manufactured tire model from Firestone on Ford trucks (158) was linked to about 140 deaths (Larry A. Beaty, personal communication). The added mortality for the case of untreated vascular variability disorders is also now documented (15); accordingly, action is overdue by those formulating guidelines for dealing with blood pressure in the clinic.

Conclusion

Natural geophysical near-weeks, aeolian quinmensals (about 5-month cycles, *Table 3*) of solar flares, geophysical half-years, the solar wind's near- and far-transyears, and decadals, didecadals, paratridecadals and semicentennians or transsemicentennians, among others, have evolved in living matter into a transdisciplinary system of coperiodisms in and around us, that are congruent by virtue of overlapping 95% confidence intervals of their periods. Each pair or set of coperiodic cycles was mapped after the rejection of the zero-amplitude (no-cycle) assumption with the uncertainties of each of its characteristics, period, amplitude, phase and, whenever possible, eventually of waveform (given by the amplitude/phase of harmonics). These multiple coexisting aeolian cycles, seen and unseen, covering a broad range of frequencies, characterize our morphology revealed by anthropometry in space and a partly novel morphology in time, as soon as a curtain of ignorance covering the normal range by such concepts as homeostasis is drawn, *Figure 49* (159). These ubiquitous cycles, some in the archaeon (91) and the human, constitute congruent signatures not only of the photic day and year, but also of the nonphotic, including gravitational and magnetic, cyclic influences upon our mental functions in particular. The non-photics can coexist and can compete with the photics and can even replace the photics, at least for a while, *Figure 50* (105). They leave their signatures in terrorism, Figure 4, military-political affairs, crime, suicide, church memberships and religious proselytism, *Figures 50A-50F*.

As to mechanisms involved, we are still learning about new cycles from old time series, back at the (cortico)steroids, with which my career started, *Figures 52A-52O*. Oscillator theories may be scaffolds, but are not the houses we build with them, or rather the cycles we map in and around us. Mapping the unseen is more challenging than mapping the seen (the photic and thermic day and year). We must learn about the influences of space weather before we can optimize what we regard as desirable – love rather than hate, philanthropy rather than crime, and peace rather than war – all carrying mapped signatures of the cosmos. The importance of this task remains an Easter challenge.

Epilogue

Many other endeavors are apparent from my bibliography, available at http://2011.geocataclysm.org/pdf/Franz_Halbergs_Bibliography-Updated.pdf (except for those that appeared after February 12, 2012). Others used their own remove-and-replace approach, independently of us, *Figure 53*. The help of all coauthors, that of my family and colleagues in particular, whether through their original active involvement or through support that made the studies possible, is gratefully acknowledged. To my colleagues I owe what became the Cornélissen-series of transdisciplinary coperiodisms (112), a page of anthropology in time. Germaine Cornélissen's contributions since her arrival in Minnesota in the 1970s cannot be separated from mine and vice versa. She and Othild Schwartzkopff described, among others, what I tried to do elsewhere (17, 26, 50, 160-167). Someday, everyone may have an affordable chance of a life mostly without VVDs, although some of us cannot help but have them transiently and some VVAs more frequently, *Figure 54* (130). In pursuit of chronobioethics, *Figure 55*, we can try to arrive, with continuous surveillance, at a life with love and not hate, and with the cosmos, to paraphrase Herschel (107), "well-disposed". Countermeasures have yet to be developed for the potentially harmful non-photic aspects of space weather, just as we learned to heat and cool in meeting the climate's seen and felt (photic and thermic) dangerous extreme conditions. But to proceed toward this goal, we need to study a unified science with its aeolian uncertainties. It seems pertinent that apparent physical-biospheric cross-validations continue to occur, as apparent for the 3 myriadennians in biodiversity finding near-matches in *Table 5*, included with the kind permission of Acad. Elchin Khalilov of Baku, Azerbaijan (168). These biological coperiodisms are seen in the spectrum of *Figure 56A*, the reconstructed models in *Figures 56B* and *56C* (globally) and the chronomic serial sections (locally in time) in *Figures 56D* and *56E*.

Table 5. Major cycles in Earth's development
(Cycles are cited from *)

N	Cycle's time span	Cycle name and reference
1	400-500 million years	Wilson cycles (V.Y.Khain, 1992), periodic formation and collapse of Pangaeas. These megacycles could be identified with cycles named after the Canadian geophysicist J.T.Wilson who discovered them first on the example of re-closing and opening of the Atlantic.
2	150-200 million years	Bertrand cycles (Khain, Seslavinsky, 1991) of M. Bertrand (Khain, 1992). He found it at the end of XIX century. In terms of recurrence in the section of multiple-age folded systems of Western Europe and North America of the same sequence of sedimentary formations: shale, flysch, molasse. He singled out four cycles - Huronian, Caledonian, Hercynian, Alpine. Of them, the three last ones are found in the literature, supplemented, however, with another cycle, Cimmerian, that appeared in the Mesozoic; the

		Huronian cycle was replaced by N.S.Shatsky with the Baikal one. Corresponding to one of the cycles of biodiversity mentioned, Shaviv, 2002.
3	140 million years	Robert A. Rohde & Richard A. Muller. Cycles in fossil diversity. NATURE | VOL 434 | 10 MARCH 2005
	60-63 million years	Even periods of large-scale continental volcanism have been shown to have this same 60-million year cycle. Robert A. Rohde & Richard A. Muller, 2005
3	30 million years	Stille cycles (V.Y.Khain, 1992). These cycles are marked with orogenic phases when fold-thrust deformations were on the rise. Again, these cycles coincided with the periodicity of changes in the intensity of tectonic deformation, island arc volcanism, granite formation and regional metamorphism. This periodicity is similar to that which is established for great fauna extinctions and regenerations linked in turn, on the one hand, with major transgressions and regressions, and on the other, with intensifications of bombardment of the Earth with large meteorites and (or) comets.
4	3-5 million years	Most pronounced are in the stratification of the global stratigraphic scale of the Phanerozoic, and definitely was the unconscious empirical basis in developing this scale. In the above-mentioned Vail curve of eustatic sea level fluctuations, this cyclicity corresponds to cycles of the third order.
5	400 thousand years	Berger et al., 1989 (changes in the eccentricity of Earth's orbit), the periodicity established by M. Milankovich and successfully used by him to explain the alternation of glacial and interglacial periods.
6	100 thousand years	Berger et al., 1989 (changes in the eccentricity of Earth's orbit), the periodicity established by M. Milankovich and successfully used by him to explain the alternation of glacial and interglacial periods.
7	41 thousand years	Berger et al., 1989 (changes in the inclination of Earth's axis of rotation).
8	19-23 (20) thousand years	Dercourt et al., 1986 (precessions). This cyclicity is also reflected in changes in lithology and thickness of extraglacial deposits, in particular, changes in the calcium carbonate and organic carbon content.

* Khain V.E., Khalilov E.N. CYCLES IN GEODYNAMIC PROCESSES: THEIR POSSIBLE NATURE - Moscow: Scientific World, 2009. - 520 p.

Acknowledgement: I am grateful to Botond Buda and the journal Folia Anthropologica for prompting me to cite personal as well as professional topics in this biographical sketch and cite others as judges of my endeavors.

Figures

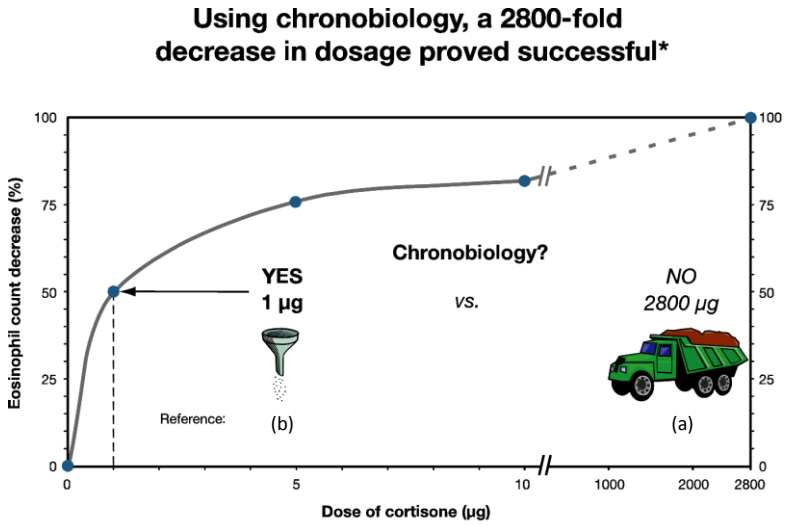


Figure 1. Gain in sensitivity from taking rhythms into account. Circulating eosinophil cell depressing activity was detected with 1 µg of cortisone when tested in the ascending phase of the circadian rhythm in the count of these blood cells (25). The increase in sensitivity of the assay is depicted by comparing the minuscule dose on the left, taking into account the rhythm, with the dose depicted as a truckload on the right, when the rhythm was "eliminated" by depressing the cell count to zero for 24 hours by 2.8 mg of cortisone used as the standard in my original bioassay in Boston (5). Using chronobiology, a 2800-fold decrease in dosage proved successful. © Halberg.

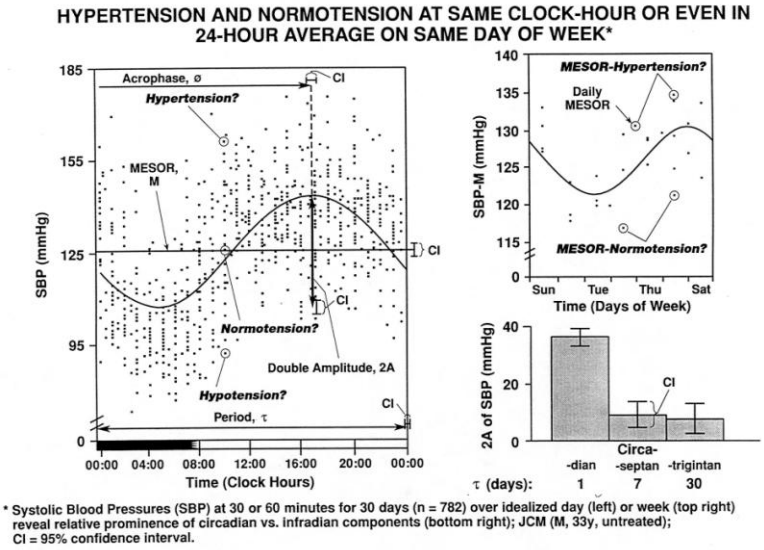


Figure 2A. Hypertension and normotension at same clock-hour on different days or even "prehypertension" or "normotension" in 24-h average on same day of the week in different weeks. © Halberg.

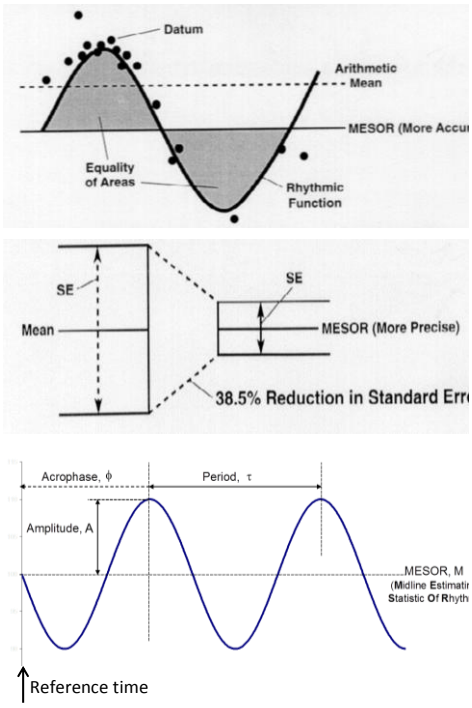


Figure 2B. Top: The MESOR is usually more accurate than the arithmetic mean, as it is less biased from sampling at non-equidistant intervals. Middle: The MESOR is usually more precise than the arithmetic mean, as it tends to have a smaller standard error (SE) since the variability accounted for by the usually prominent rhythmic pattern does not enter the error term. Bottom: Illustration of a cosine function identifying four parameters of the oscillation: MESOR, period, amplitude, and acrophase. © Halberg.

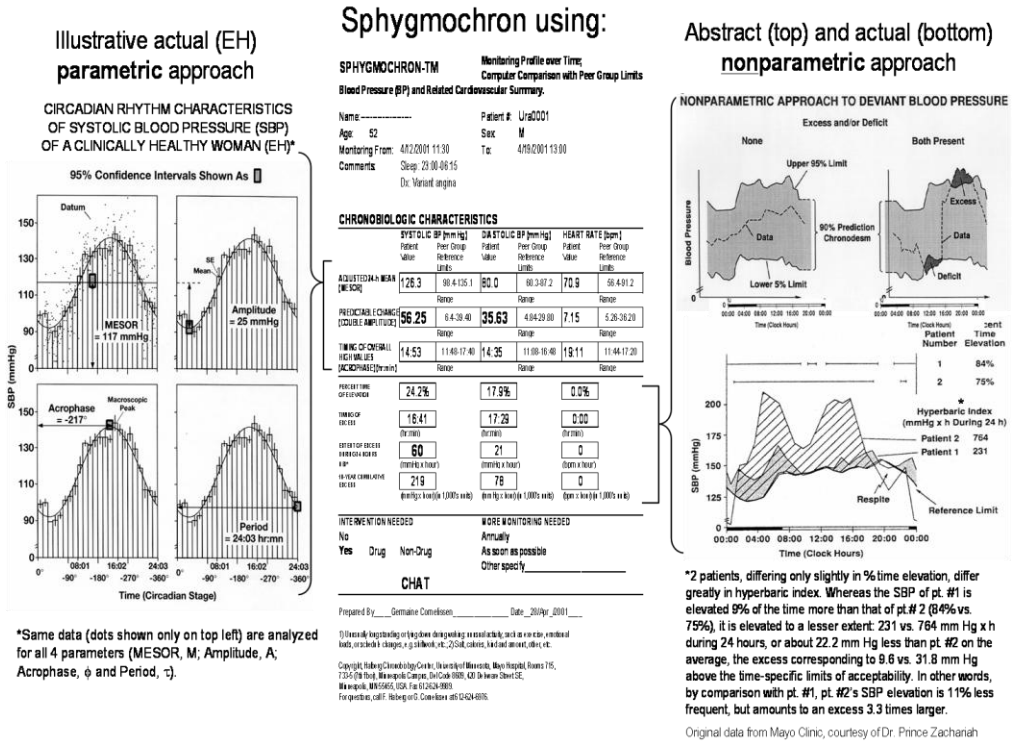


Figure 2C. Illustrative parametric (left) and non-parametric (right) approach bracket a sphygmochron (middle) from a MESOR-normotensive man with CHAT, a first tentative diagnosis requiring additional monitoring. After data covering preferably at least 7 days of

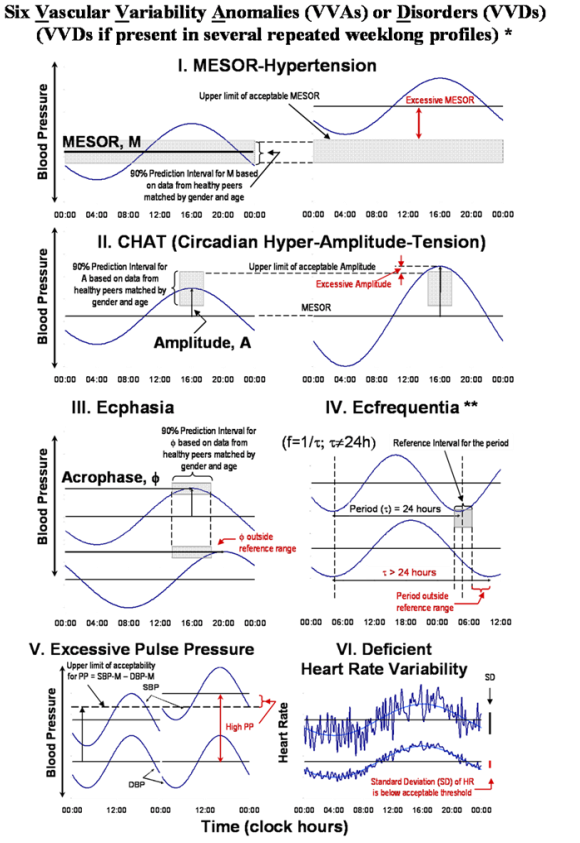
blood pressure (BP) and heart rate (HR) are downloaded from the e-mail into a computer for analysis, the following results are provided (since the 1990s and currently cost free from corne001@umn.edu) for the patient as well as for the care provider:
1. A list of actual measurements and the times at which they were obtained.
2. A plot of data as a function of time, shown together with the time-specified prediction intervals (PIs) of acceptability for systolic (S) and diastolic (D) BP and HR characteristics.
3. A data summary, and a report of any BP and/or HR excess in consecutive 3-hour intervals. This part of the report may be accompanied by a "rhythmometric summary", which is just a more technical form from which the information is derived to prepare the:
4. "Sphygmochron". A sample "sphygmochron" (center) illustrates how results are being reported. First, above, the participant's name is kept confidential; a codename is used instead. Gender and age are listed, along with the date and time at which monitoring started, and for how long data were collected. The numerical report consists of two parts labeled "Characteristics" (parametric results) and "Indices of Deviation" (non-parametric results). In each case, results are shown for SBP (when the heart contracts) on the left, DBP (when the heart relaxes) in the middle, and HR on the right. Under "parametric results", a mathematical model of a smooth curve is fitted to the data to assess their circadian variation, which is primarily characterized by four numbers shown in the left-hand section of the graph, one of which, the period, covers with its uncertainty the precise 24 hours, so that the other 3 numbers are given from the fit of a 24-hour cosine curve. One characteristic, called the "MESOR", is the average value around which values fluctuate. It is very similar to the mean value, but yields more reliable results when the data are not collected at precisely regular intervals, and has a smaller error when the data are equally spaced. Another characteristic, called the "double amplitude", is a measure of the predictable change occurring within a day, from the overall low values found usually during sleep to the high values during the daily active span. The third characteristic, called the "acrophase", is a measure of the time when overall high values are likely to recur each day. For each of the three characteristics ("parameters"), the participant's value is compared to a range of acceptable values, derived from data provided by clinically healthy people of the same gender and age group as the participant. For instance, in the example shown here in Sphygmochron, the average SBP, the DBP and all other parameters are within the rectangles, indicating the range of acceptable values except for the double amplitudes of SBP and DBP. Under "non-parametric results", the participant's data are compared by computer with time-specified reference values, also derived from chronobiological archives on clinically healthy subjects matched by gender and age. For this analysis, all data are stacked over an idealized 24-hour day. Whenever a given person's profile exceeds the limits of acceptability of peers, the data are marked as being excessive or deficient. The "percentage time of elevation" reports the relative incidence of excessive values during a 24-hour day. It is common to have occasional high values, but in the example herein there is reason for concern. The next item, the time of excess, becomes useful when drug treatment should be timed prior to the peak in excess.

Excessive values may either be barely above the limit or in turn can be very much higher than the limit. It is therefore important to express the extent of deviation by the "area under the curve", that is the area between the values when they exceed the limit and this limit itself. Empirically, it has been shown that excess up to about 50 (mmHg x hour during 24 hours) may still be acceptable and accountable for by daily worries and/or and/or physical activities. In the case summarized, the HBI is 60, in bold, and if confirmed in the next 7/24 profile, a reason for treatment.

On the top right, an abstract illustration of excess and deficit is accompanied below by 2 cases that are similar in terms of percent time elevation. They are very different in terms of

hyperbaric index. In patient #2, although the percent time elevation is 9% smaller than that in patient #1, the hyperbaric index is several times larger.

The "timing of excess" can be used as a guide to time the administration of non-drug or, if need be, of drug treatment once there is BP excess above 50 (mmHg x h during 24 hours) and/or an elevation in MESOR, taking into account the chronopharmacokinetics of the drug prescribed. When, e.g., a tentative diagnosis of MESOR-normotension with CHAT is made, with insight into information provided on the questionnaire given to the participant with the monitor, as a first step, additional analyses may be carried out. Additional monitoring is recommended to check on any abnormality detected during the first monitoring, and if confirmed, the need for intervention is reported to the person monitored so that it can be reported to the health care provider. In one case summarized elsewhere, the follow-up 7-day monitoring showed that CHAT persisted for both SBP and DBP, while the MESORs were again acceptable. Thus, the diagnosis of CHAT with MESOR-normotension was confirmed. Consultation with a health care provider was strongly and urgently recommended. In two cases of CHAT without an elevation of the BP MESOR, when such recommendations were ignored, catastrophic disease and high cost occurred, a myocardial infarction in a man or eclampsia in a pregnant woman with pressures of 115/67 mmHg (SBP/DBP), leading to the delivery of a very premature boy hospitalized for 26 months at a cost of $1 million U.S. © Halberg.



* Validated by chronobiologic analysis of around-the-clock 7-day/24-hour records of measurements at 1-hour or shorter intervals, interpreted in the light of time-specified reference standards qualified by gender and age. ** Ecfrequentia: short for frequency (f) alteration (e.g., desynchronization) that can be Dysfrequentia when associated with symptoms and/or persisting in repeated consecutive 7-day records.

Figure 2D. Abstract limits for acceptable I. MESOR and II. amplitude (left, first 2 rows, and upper curves in bottom 2 rows) for III. acrophase, IV. frequency (period), V. pulse pressure and VI. heart rate variability, associated with blood pressure and heart rate surveillance and their

corresponding vascular variability anomaly (VVA) descriptions.

I. MESOR-hypertension (MH), can be systolic (S) (S-MH), diastolic (D) (D-MH) or both (SD-MH), or mean arterial (MA-MH), demonstrated parametrically (by cosine fitting).

II. Circadian Hyper-Amplitude-Tension (CHAT), which can also be systolic (S-CHAT), diastolic (D-CHAT), both (SD-CHAT) or mean arterial (MA-CHAT), etc. (by cosine fitting).

III. SBP, DBP or SDBP ecphasia (odd timing of the circadian rhythm of BP but not of that in HR) (by cosine fitting).

IV. Ecfrequentia (altered τ of the circadian rhythm, including multifrequentia) (by cosine fitting).

V. Excessive pulse pressure (EPP), when the difference in the MESORs of SBP and DBP for adults exceeds 60 mmHg, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually) with disease-free long-life outcomes) specified further by gender, age, ethnicity and geography.

VI. A deficient HR variability (DHRV), defined as a standard deviation of HR less than 7.5 beats/minute, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease free long-life outcomes) specified further by gender, age, ethnicity and geography. © Halberg.

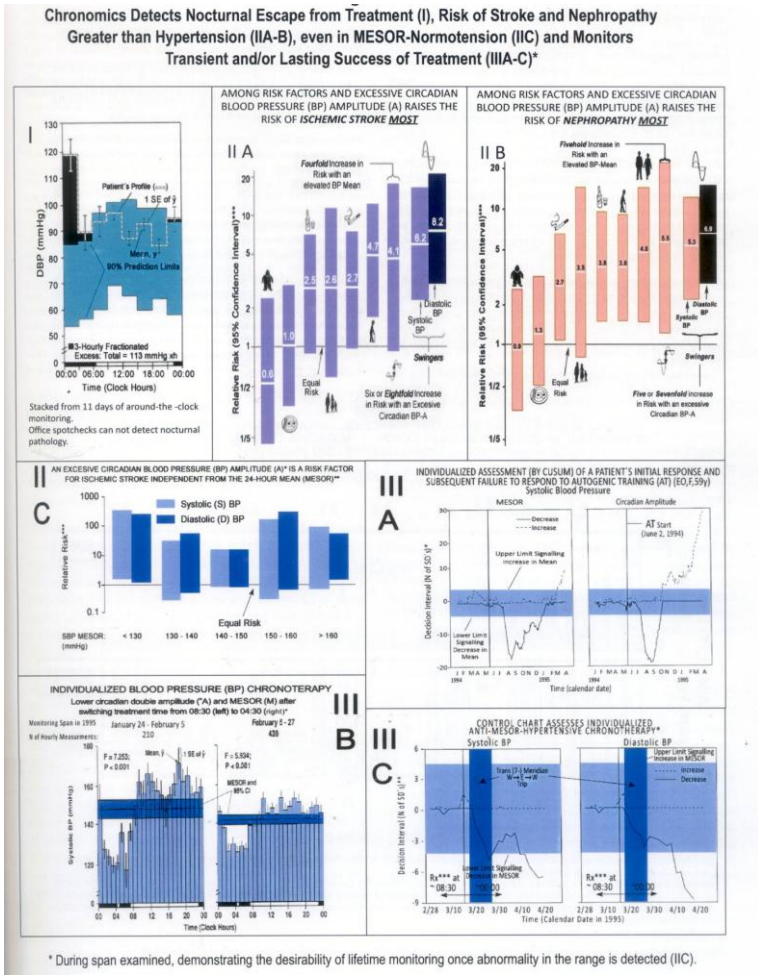


Figure 2E. Illustrative results supporting the need for continued surveillance and for a chronomic analysis of blood pressure series.

I: Nocturnal hypertension: data stacked from 11 days of around-the-clock monitoring. Office spotchecks cannot detect nocturnal pathology. II A: Among risk factors, an excessive circadian BP amplitude (A) raises the risk of ischemic stroke most. II B: Among risk factors, an excessive circadian BP-A raises the risk of nephropathy most. II C: An excessive circadian BP-A is a risk factor for ischemic stroke independent from the 24-hour mean (MESOR). III A: Individualized assessment (by CUSUM) of a patient's initial response and subsequent failure to respond to autogenic training (AT) (EO, F, 59y). III B: Individualized BP chronotherapy. Lower circadian BP-2A and MESOR after switching treatment time from 08:30 (left) to 04:30 (right). III C – Control chart assesses individualized anti-MESOR-hypertensive chronotherapy. Chronomics detects nocturnal escape from hypotensive treatment taken in the morning (I above) and conditions such as CHAT, associated with a risk of stroke and nephropathy greater than hypertension (IIA, B), even in MESOR-normotension (IIC), and monitors transient and/or lasting success of treatment (IIIA-C). Merits are:

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

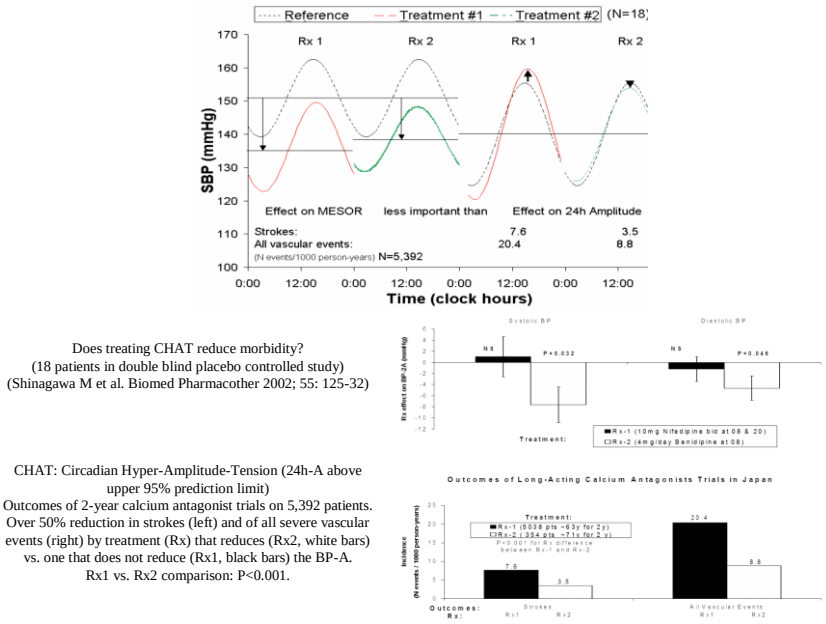


Figure 2F. Benidipine (taken once a day upon awakening, Rx2) was found in large Asian

clinical trials to be associated with better outcomes than nifedipine (taken twice a day, in the morning and in the evening, Rx1). Reducing the incidence of CHAT may be the reason accounting for the difference (almost by a factor 2) in outcomes, whether strokes or all cardiovascular events are considered. © Halberg.

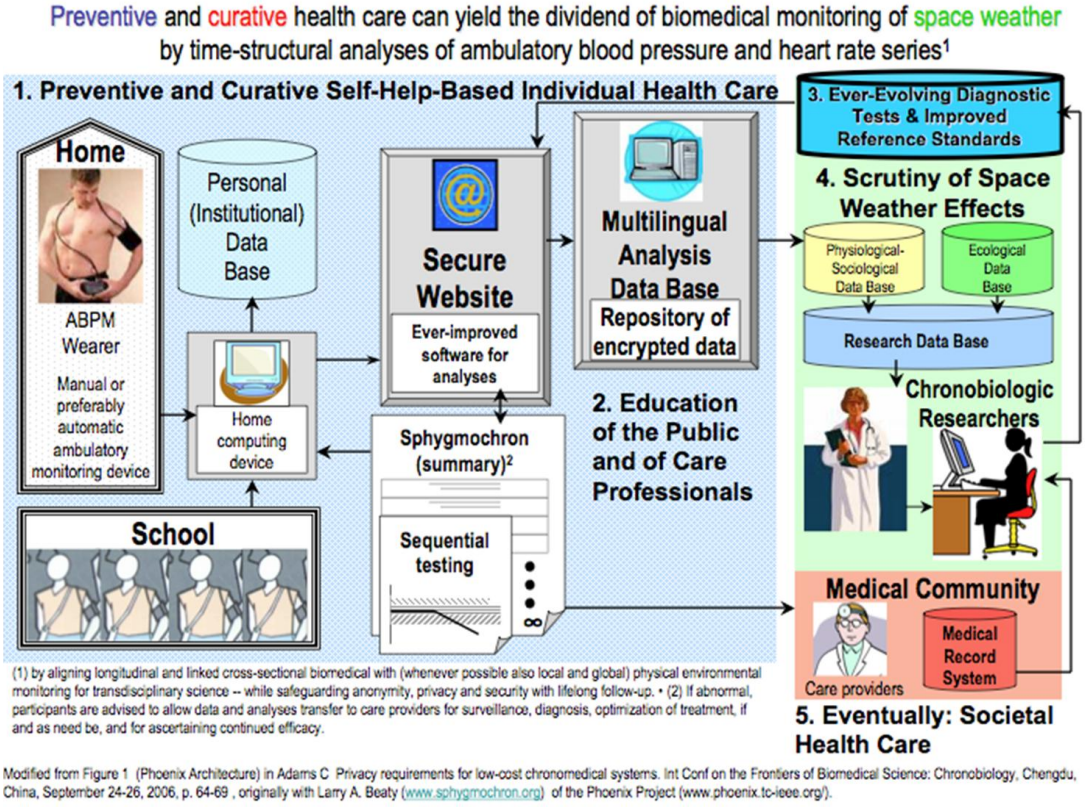


Figure 2G. Concept of an international multilingual website serving all comers worldwide, as a project on The BIOsphere and the COSmos, BIOCOS, now does on a small scale (left half of graph) with the data available to care providers (right bottom) and (after aligning with epidemiological data on natality, morbidity and mortality and on crime and terrorism as well as with philanthropy and physical environmental data) for research on medical and broader problems with special reference to effects of space weather. The Phoenix Group of volunteering electrical and electronic engineers from the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (http://www.phoenix.tcieee.org) is planning on developing an inexpensive, cuffless automatic monitor of blood pressure and on implementing the concept of a website (www.sphygmochron.org) for collection and analysis of data collected with these instruments. © Halberg.

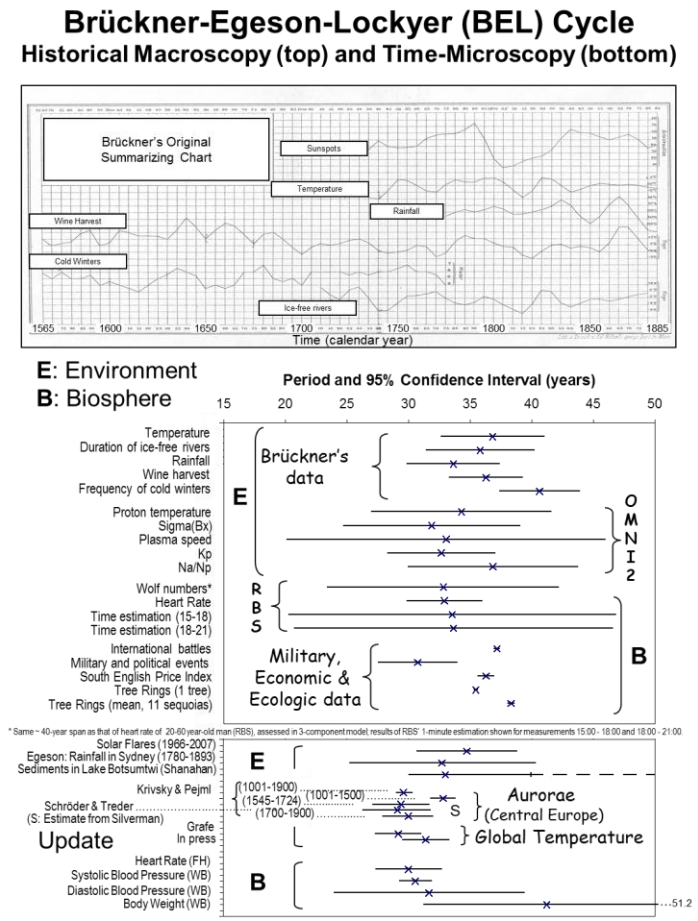


Figure 3A. Display of original climate data (top) and map of environmental-biospheric paratridecadal Brückner-Egeson-Lockyer (BEL) cycles (bottom). The BEL cycle originally found in Brückner's data (first 5 point-and-interval estimates of the period) is also detected by spectral analysis of military, economic and ecological data and in physiological data from RBS and from two other men (FH and WB), as well as in many other population phenomena, the mechanisms of which become available to study on individuals for investigators who try to plan beyond their lifespans. An about 33-year cycle was reported as a spectral peak by Shanahan et al. (Science 2009; 324: 377-380) who studied sediments in Lake Botsumtwi in Africa. The spectral coherence peak covers periods of 30 to 50 years (full length of uncertainty bar shown in graph) but includes a double peak, the second peak corresponding to another spectral peak at 42 years. The tick mark at 40 years corresponds to the small trough on the published coherence graph between the two peaks. Silverman (Rev Geophys 30: 333-351, 1992) was first to report an about 33-year spectral peak in aurorae (S in graph) but did not provide uncertainty estimates. The latter are derived for aurorae observed in Central Europe as compiled by Krivsky and Pejml during 1001-1900, analyzed globally and during different spans corresponding to varying average numbers of reported aurorae as technology to detect them improved. The span from 1545 to 1724 was of special interest as it allowed a comparison with an independent set of data reported by Schroeder and Treder. © Halberg.

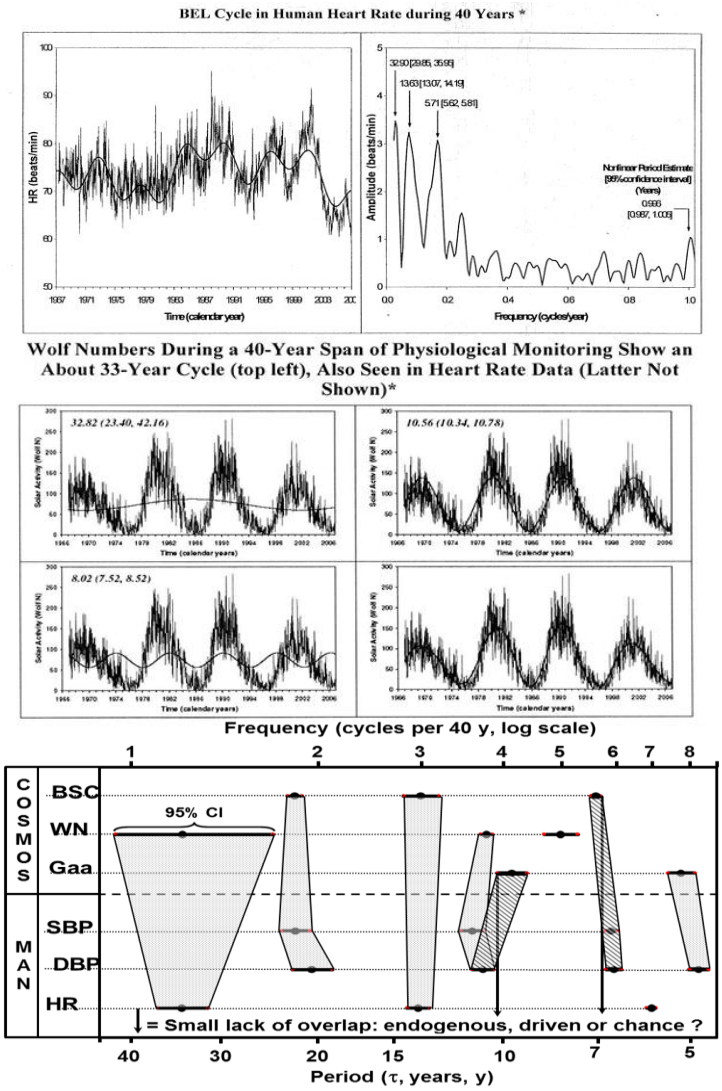


Figure 3B. Top: time series of weekly mean heart rate data for a clinically healthy individual, RBS (a), and its spectrum (b). Middle: Original time series of sunspot number (Wolf's number, *W*) and superposed spectral components with periods (a) 32.82 (top left), (b) 10.56 (top right), (c) 8.02 (bottom left), and (d) its three-component model (bottom right curve). The spectral components are listed with 95% confidence intervals in parentheses after the period values. Bottom: Influence of solar activity on the human cardiovascular system: the congruence of natural and physiological cycles with periods from several years to several decades. (*1*) cycle of change in the polarity of solar magnetic field (Hale's cycle), BSC; (*2*) relative sunspot numbers (Wolf's numbers), WN; (*3*) geomagnetic index *aa*, as determined from data of antipodal observatories in Greenwich and Melbourne, Gaa; (*4*) systolic arterial pressure, SBP; (*5*) diastolic arterial pressure, DBP; and (*6*) heart rate, HR. The horizontal length of black columns reflects 95% confidence intervals for respective periods. Thin near-vertical linking lines and shading indicate congruent periods. © Halberg.

Additions and Subtractions (loss and replacement) of Spectral Components in and around us, Based on 14,579 Cases of Terrorism in 39 years (B and A, row 3) and Systolic Blood Pressure (C, row 2)

Aeolian behaviors of solar wind speed (SWS), geomagnetism (aa), and terrorism (MIPT) reveal a far-transyear in the absence of a dominant calendar year (*); about 1.33-year component in terrorism lags with intermittent statistical significance behind SWS and aa

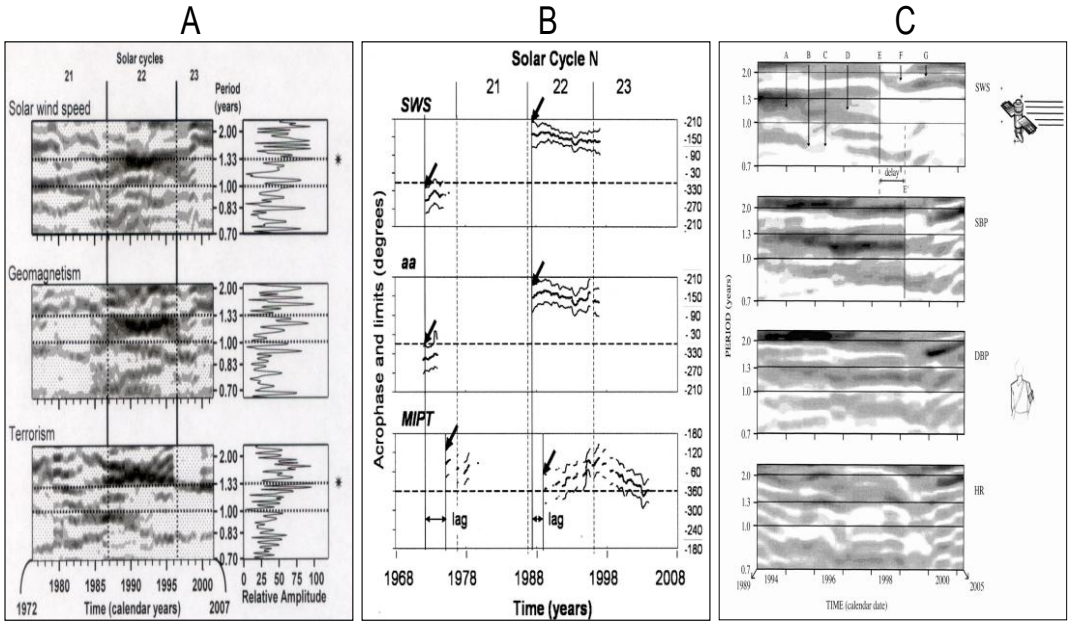


Figure 4. Just as removal and replacement of a gland led to endocrinology, so biological consequences of the loss of environmental spectral components are critical to chronomics, the study of chronomes (time structures) in and around us. The drifting, bi- or trifurcation, disappearance and reappearance of a component with a given frequency and, when present, the waxing and waning of its amplitude, visualized in A and C, is in keeping with external driving of an individual (C) and of a population (A and B). Note components with neighboring frequencies waxing at or near a transyear component in solar wind speed (top of A and of C), geomagnetism (second row of A), and in 39 years of terrorist activity (bottom of A), an association supported by an independent method in B (by the statistical significance of the fit of a 1.3-year far-transyear to interplanetary (SWS) and terrestrial (aa) magnetism and to terrorism. Analysis in A is glocal insofar as it is based on the entire series in the spectral window on the right (global) and in sections of the series in the gliding windows on the left (local). Analyses only on sections of the time series are local in B (complementing the global counterpart, as seen on the right of A) and local in C.

C shows time courses of the frequency structures of the speed of the solar wind (SWS) (top) and of an elderly man's (FH) systolic and diastolic blood pressure and heart rate, SBP, DBP and HR (rows 2-4, respectively), examined by gliding spectral windows. Human systolic (S) blood pressure (BP) selectively resonates with solar wind speed (SWS) (top 2 sections). No obvious resonance, only minor coincidence of apparent change, is apparent to some in diastolic (D) BP or heart rate (HR) (bottom 2 sections). Aeolian rhythms in gliding spectra of SWS and SBP change in frequency (smoothly [A] or abruptly [B,C,D], bifurcating [D,F] and rejoining [G]; they also change in amplitude (B) (up to disappearing [C,E] and reappearing). © Halberg.

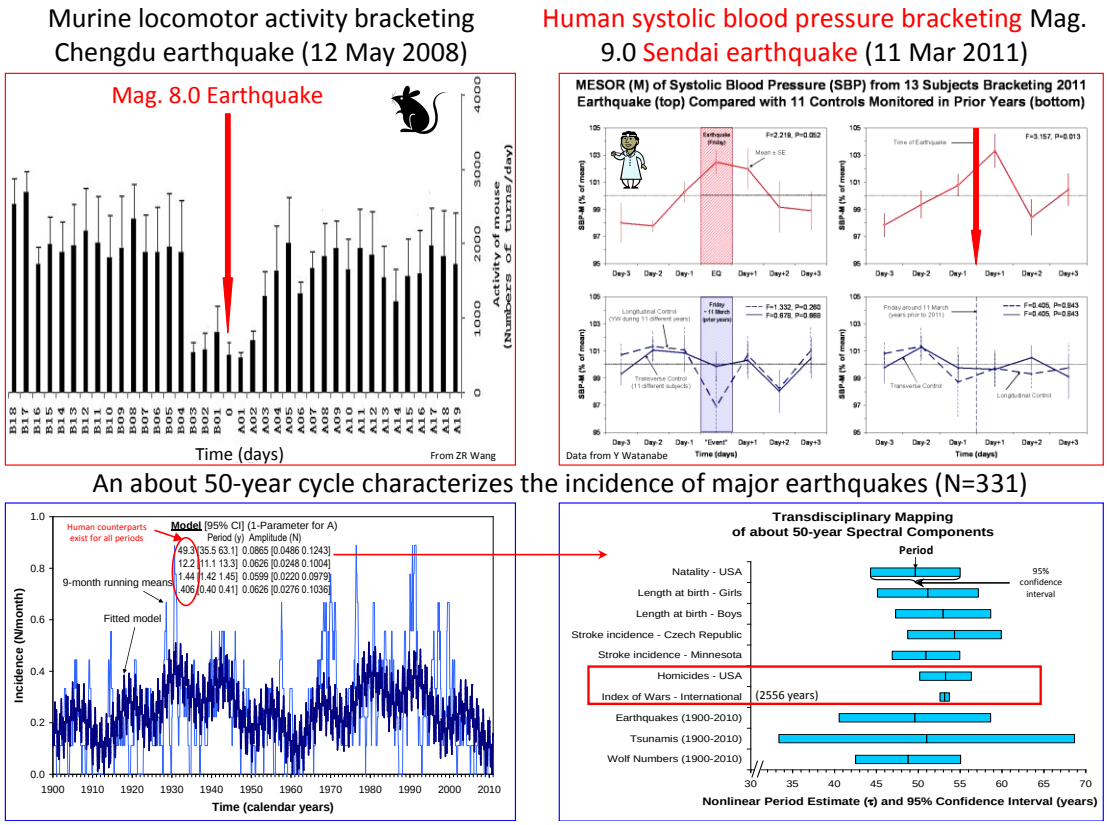
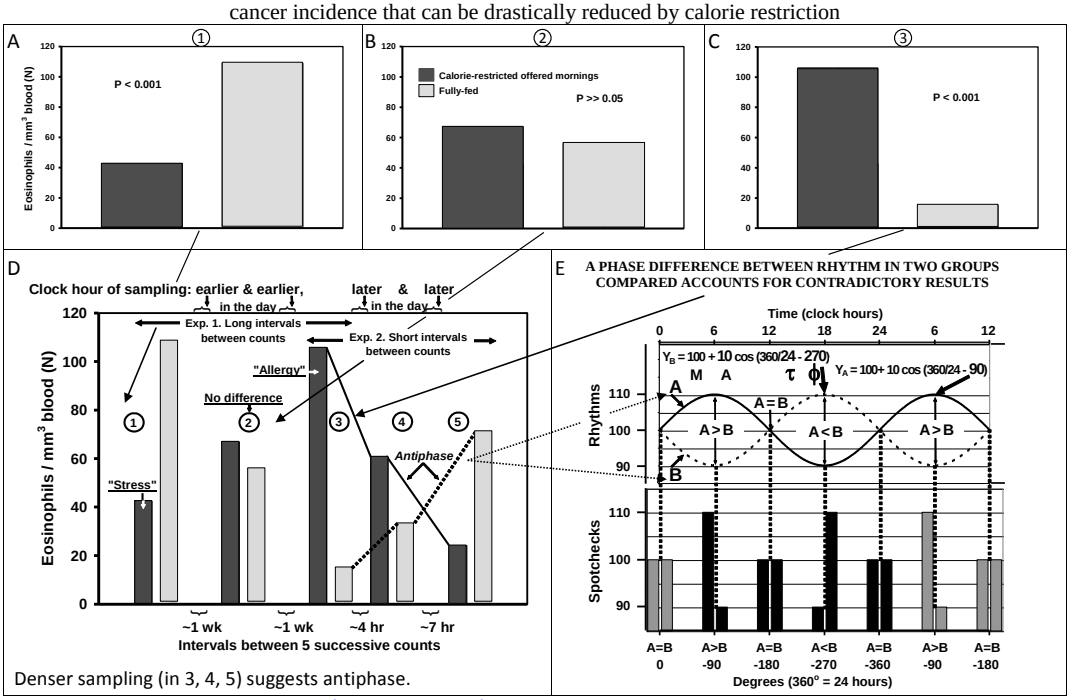


Figure 5. Biospheric contributions to the understanding, if not prediction of earthquakes. Upper left: Locomotor activity of some of the mice telemetered around the clock was statistically significantly decreased starting 3 days prior to the magnitude 8.0 earthquake in Chengdu, China on 12 May 2008 (data of Zhengrong Wang). Upper right: Human systolic blood pressure started increasing 2 days prior to the magnitude 9.0 earthquake in Sendai, Japan on 11 March 2011, documented on the basis of weeklong records of around-the-clock ambulatorily obtained data from 13 Japanese (data of Yoshihiko Watanabe). Similar records from longitudinal and transverse controls differ in their time course, suggesting that the trend observed before the earthquake was related to it rather than being a feature of an anticipated weekly pattern. Lower left: The monthly incidence of major earthquakes since 1900 is characterized by the presence of cycles with periods of about 49.3, 12.2, 1.44, and 0.41 year(s), given with their uncertainties in parentheses. Lower right: The prominent about–50-year cycle is also documented in physiology, pathology, societal upheavals and space weather. Nonlinearly estimated periods are displayed with their 95% confidence intervals shown as the length of corresponding horizontal bars. © Halberg.

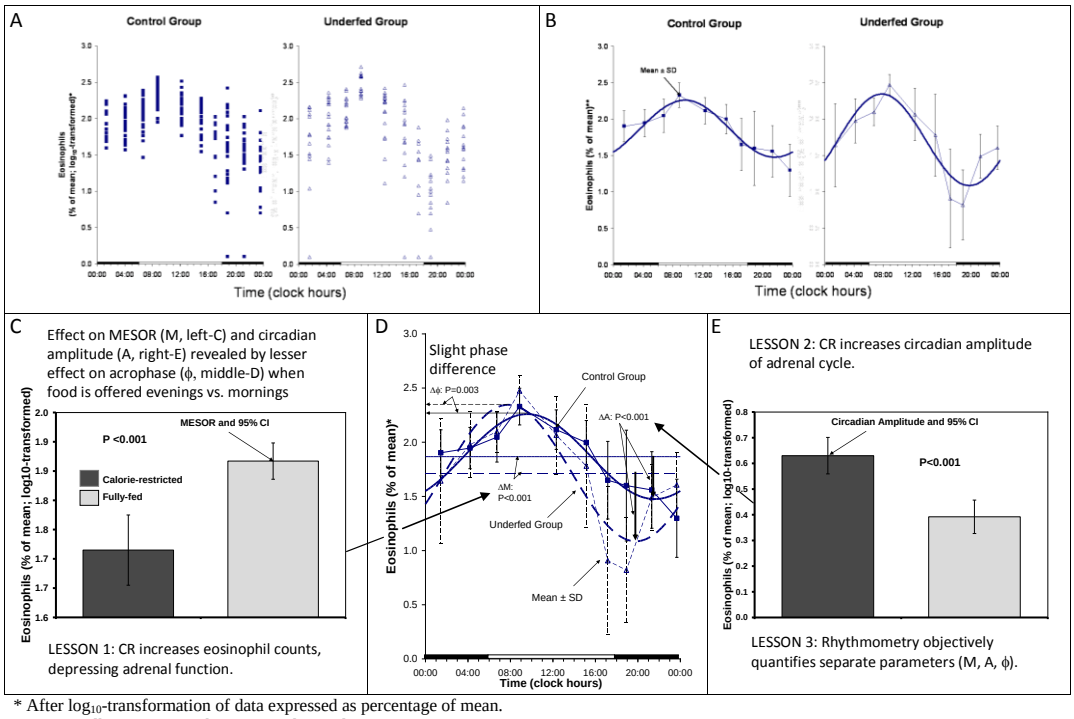
Confusing results, that could wrongly be interpreted as "stress" or "allergy", are accounted for by the action of food (offered mornings) and light as competing synchronizers of circulating eosinophils in C_3H mice with high breast cancer incidence that can be drastically reduced by calorie restriction



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

Figure 6A. Importance of rhythms in assessing intervention effects, illustrated in relation to stress or allergy. A. Eosinophil counts seem to be lowered by fasting (and/or stress), when a 50% reduction in dietary carbohydrates and fats (with proteins, vitamins, and minerals similar to control group) was fed in the morning to C_3H mice (dark column). (In this model, the naturally high incidence of breast cancer is lowered by a diet reduced in calories and by ovariectomy, not shown.) The result could have been interpreted as an adrenocortical activation and then assessed by eosinophil depression, with applications for treating breast cancer and for prolonging life. Steroids that depress eosinophil cell counts and perhaps mitoses could be a mechanism through which caloric restriction and ovariectomy act in greatly reducing cancer incidence. This tempting inference was never published. B. In view of the importance of this finding for the etiology of cancer, results were replicated on a larger group of animals; one week later, a follow-up study with more animals started at an earlier clock-hour, yielded confusing results, showing no statistically significant difference between the two groups of mice. C. After another week, another study starting at an even earlier clock-hour yielded results opposite to those in the first experiment when considered alone. These findings in C in themselves could have been interpreted as an allergic response, certainly contrary to the "stress" response in A. D. Sampling at intervals of a few hours in the third study, the stages called 4 and 5, hinted at the reason for the confusion: by sampling at different clock-hours, two groups of mice were found to be characterized by a circadian rhythm with different phases. Opposite effects thus became predictable. E. Abstract illustration of two circadian rhythms in antiphase. Differences in opposite direction or no effect are then anticipated from sampling at different clock-hours. © Halberg.

Calorie-restricted meal offered evenings only slightly advances phase (no antiphase versus controls, as seen with morning meals), lowers MESOR and amplifies circadian eosinophil rhythm in C_3H mice with high breast cancer incidence that can be reduced by calorie restriction (CR)



* After $\log_{10}$-transformation of data expressed as percentage of mean.
From Halberg F & Visscher MB. Endocrinology 1952; 51: 329-335.

Figure 6B. Effect of food restriction on circulating eosinophil counts in mice. Follow-up study on *Figure 6A*, with a phase difference greatly reduced by offering the restricted diet in the evening. A. Even after $\log_{10}$ transformation of the data expressed as percentage of mean, great interindividual variability is apparent in the raw data. B. Plots of timepoint mean for mice in each group reveal different circadian patterns. C-E. Parameter tests quantify differences, indicating that calorie restriction is associated with a lower MESOR (C-D), a larger circadian amplitude (D-E), and only a slight difference in acrophase (D). The difference in acrophase in this study, where calorie-restricted mice were fed in the evening, is much smaller than the almost-antiphase observed in prior studies (*Figure 6A*), where calorie-restricted mice were fed in the evening. © Halberg.

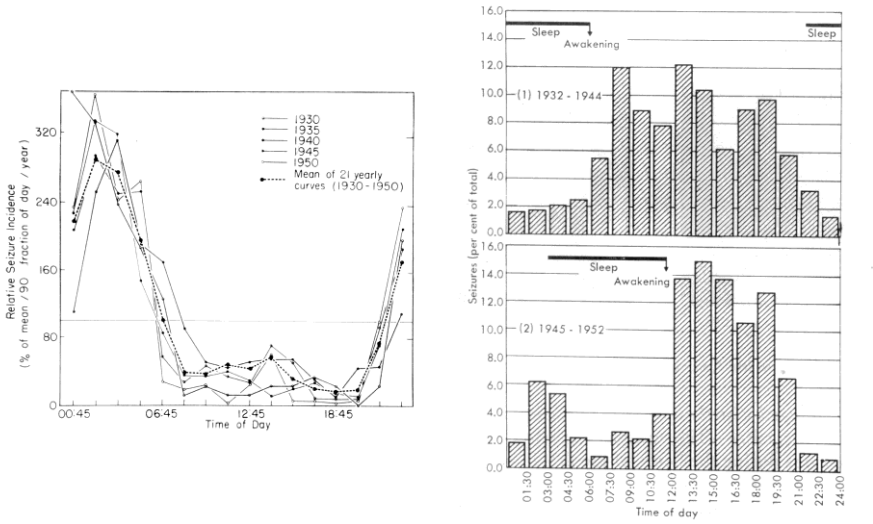


Figure 7. Left: Unequal distribution of epileptic seizures during the hours of the day in a case observed for 20 years. Night-type.
Right: Unequal distribution of epileptic seizures during the hours of the day on two routines, maintained for many years. Day-type. Note change in seizure distribution following change in routine. Daily sleep-wake routine may be regarded as the environmental synchronizer of seizure rhythm; clock-hour as such does not matter in determining times of occurrence of seizures. © Halberg.

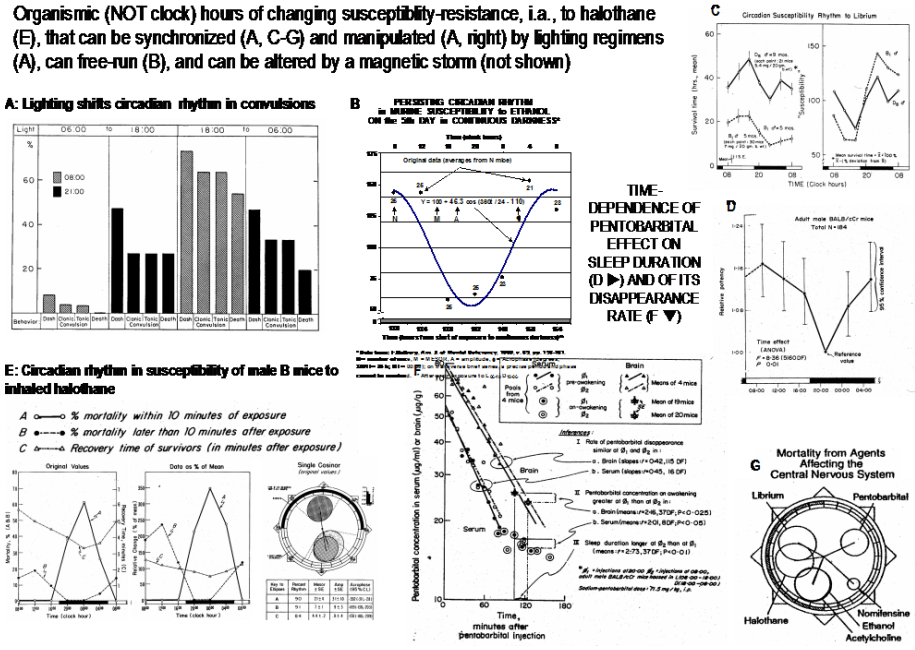


Figure 8. Part of the history of susceptibility rhythms in the response of the mammalian central

nervous system (extreme "phase responses"). By 1955, the response to noise (>104 decibels [dB] >0.0002 dynes/cm^2 rms pressure) was shown to be circadian stage-dependent in mice of the susceptible I strain, so that the convulsive risk by day was 11% and by night 65% in one group of young mice and 0% by day and 85% by night in another group (35). There were more convulsions and more deaths from exposure to bells in a tub at the beginning of the daily dark span as compared to exposure of animals of the same inbred strain, gender and age, the other at the start of the daily light span in mice kept in light from 06:00 to 18:00, alternating with darkness (not shown). This was confirmed in a follow-up study, section A (36). Again, convulsions and death occurred in a stimulator with exposure to ~117 dB >0.0002 dynes/cm^2 rms pressure at 21:00, but no deaths and fewer convulsions with exposure at 08:00, as seen in the left half of section A. The right side of section A shows not only that the timing of this susceptibility rhythm (on the fourth day after reversal of the lighting regimen) can be shifted along the 24-hour scale (can apparently be reversed) and that, at the time investigated (perhaps as a transient), there is an overall increase in susceptibility.

Section B, a 6-timepoint phase response curve in continuous darkness, shows the persistence of a response rhythm of mice, gauged by the survival time of mice after injection of a fixed dose of ethanol. Sections C and D show further phase response curves to Librium and pentobarbital, i.e., drug-related results under conditions of a 12-hourly alternation of light and darkness. Time-macroscopic (E, left and middle) and time-microscopic (E, right) assessment of parameters of a rhythm in susceptibility to halothane given as an amplitude by the length of a vector and as the acrophase by the vector's direction, with their elliptical 95% confidence regions as indications of uncertainties. For the acrophase, its 95% confidence limits (CL) are obtained by tangents to the error ellipse. Section F shows pentobarbital concentration in brain and serum of mice as a function of time after injection at circadian phases of short sleep duration (φ1) and long sleep duration (φ2). Section G shows, with their uncertainties, differences in the timing of phase responses to different agents affecting the mammalian central nervous system (72). © Halberg.

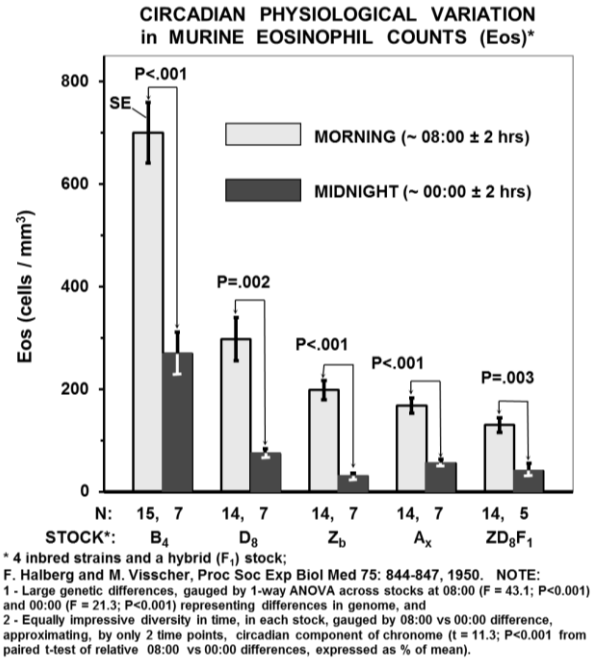


Figure 9. Circadian physiological variation in murine eosinophil counts (Eos). In four inbred

strains and a hybrid F_1 stock (47). Note large genetic differences anchored in the genome, namely 1. across stocks at 08:00 gauged by one-way ANOVA ($F=43.1$; $P < 0.001$) and 00:00 ($F=21.3$; $P < 0.001$), and 2. equally impressive diversity in time, in each stock, gauged by 08:00 vs. 00:00 difference, approximating, by only two timepoints, the circadian component of chronome ($t=11.3$; $P < 0.001$ from paired t-test of relative 08:00 vs. 00:00 differences, expressed as percent of mean). The ever-present within-day difference can differ among stocks of mice. © Halberg.

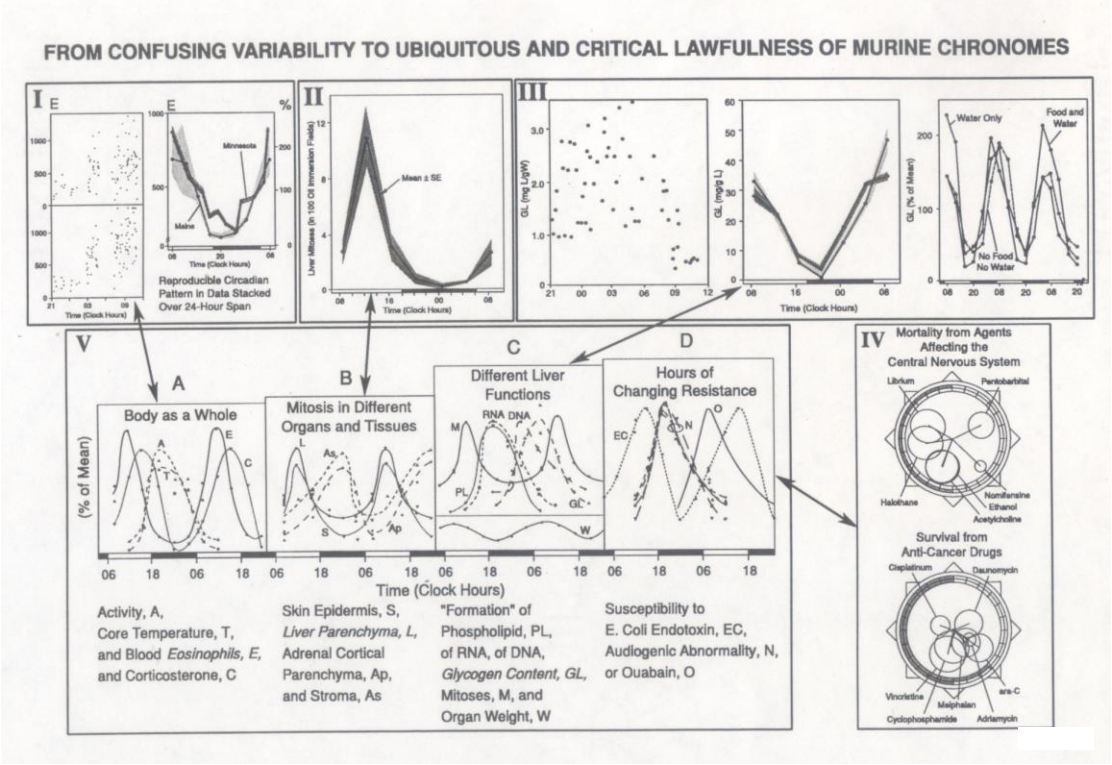


Figure 10. From confusing variability to the ubiquitous and critical lawfulness of murine chronomes (time structures). Time plots of original values (dots) of variables such as blood eosinophils (E) (I, left) or glycogen content (III, left) reveal great variability, confusing at first, until the data are processed by relatively simple statistical techniques such as averaging and stacking over an idealized 24-hour span corresponding to an anticipated 24-hour synchronized periodicity. Once this is done and the results are displayed as a function of time, they show the time-macroscopic ubiquity of circadians. The data averaging for different hours of the day also reveals differences in the time course (in phase) of different functions of a given organ such as the liver (VC), of cell division (mitosis) in different organs and tissues (VB) and of different variables at the level of the body as a whole (VA and D). The structure of the circadian system becomes apparent by the application of the methods of chronobiometry: the circadian variation in blood eosinophils determined years apart in two laboratories as far apart as Minnesota and Maine is closely reproduced (I, right half). The lawfulness of the circadian variation yielded by the application of chronobiologic techniques is also revealed for the drastic changes in liver glycogen content (III, middle). In this case, a circadian rhythm in the liver's glycogen is seen to persist under conditions of starvation and dehydration, with little if any alteration in the dynamic rhythm characteristics, as compared to usual ad lib conditions, once the data are

expressed as a percentage of the overall mean, III, right.

After a prominent circadian rhythmicity was found at different levels of organization, several series of experiments were carried out under rigorously standardized laboratory conditions in order to investigate the effect of a single physical stimulus such as exposure to noise. Outcomes were as different as no response, convulsion or even death, as a function of the circadian stage at which the organism was exposed to noise. Whether the stimulus was audiogenic or the exposure to an endotoxin, or to a drug such as ouabain, or to whole-body irradiation or to other physical or chemical agents, predictable changes were found as a function of the circadian stage at which the stimulus was applied, albeit with differences in the timing of these susceptibility-resistance rhythms to different agents. The hours of changing resistance were thus uncovered, and the times of overall largest response by the organism to a fixed stimulus applied at different rhythm stages mapped (Figure I/VD). Applications followed after cosinor analysis to attempt to assess the uncertainties involved in timing, obtained by drawing tangents to the 95% confidence ellipses (IV). Prominent susceptibility rhythms were documented in the experimental laboratory, as illustrated here for the case of the mortality from agents affecting the central nervous system and for the case of the survival from (tolerance of) toxic doses of anticancer drugs. In each case, the nonoverlap by the elliptical 95% confidence region of the center of the circular plot (pole) can be interpreted as the presence of a statistically significant circadian rhythm in the susceptibility of the organism to each of these different agents. The orientation of the directed line (vector) indicates the time of acrophase that is the time of the largest anticipated response. Such charts are helpful in guiding the timing of the administration of the various agents so mapped. The chronotherapy of cancer (*Figures 17A* and *17B*), guided by the marker tumor temperature, is one critical application resulting from this work. © Halberg.

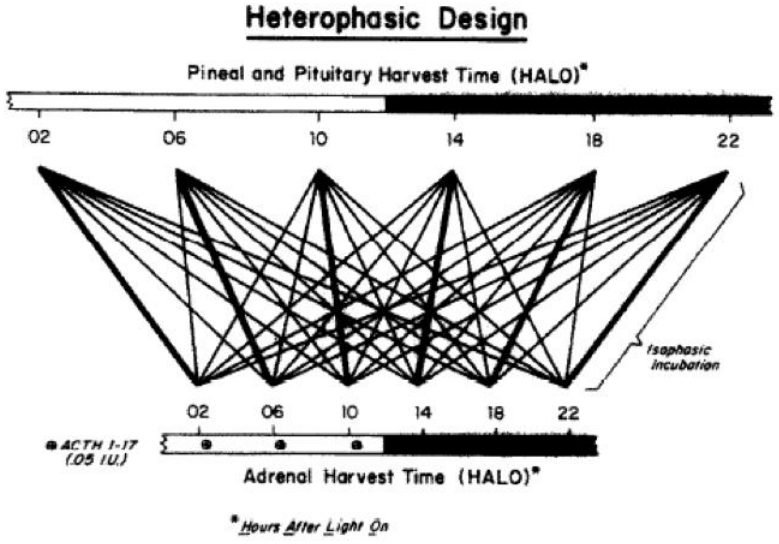
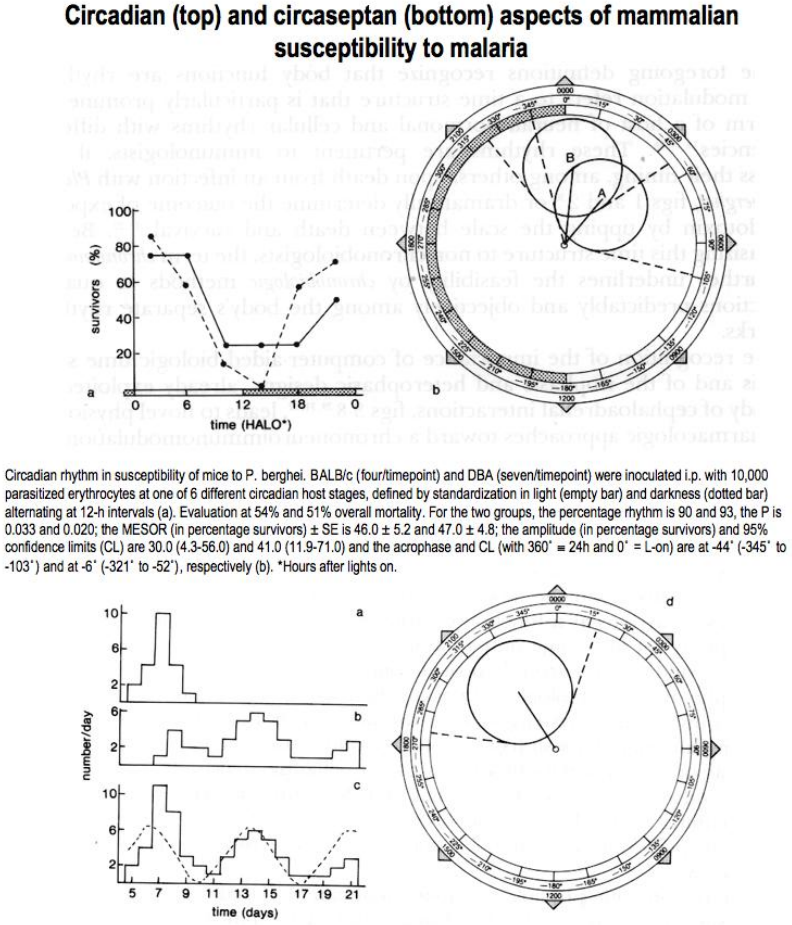


Figure 11. Work concomitantly at each of 6 circadian stages 4 hours apart became possible by separate chambers housing rodents standardized for at least 3 weeks on 6 separate lighting regimens also staggered by 4 hours, so that light, alternating with darkness every 12 hours, went on at midnight in one chamber and at 04:00, 08:00, 12:00, 16:00 or 20:00 in 5 other chambers, each containing rodents with core temperature telemetry so that circadian stage could be validated. Tissues not only from a given stage but also from the 5 other stages could thus be obtained, e.g., for incubation studies. © Halberg.



Circadian rhythm in susceptibility of mice to P. berghei. BALB/c (four/timepoint) and DBA (seven/timepoint) were inoculated i.p. with 10,000 parasitized erythrocytes at one of 6 different circadian host stages, defined by standardization in light (empty bar) and darkness (dotted bar) alternating at 12-h intervals (a). Evaluation at 54% and 51% overall mortality. For the two groups, the percentage rhythm is 90 and 93, the P is 0.033 and 0.020; the MESOR (in percentage survivors) ± SE is 46.0 ± 5.2 and 47.0 ± 4.8; the amplitude (in percentage survivors) and 95% confidence limits (CL) are 30.0 (4.3-56.0) and 41.0 (11.9-71.0) and the acrophase and CL (with 360˚ ≡ 24h and 0˚ = L-on) are at -44˚ (-345˚ to -103˚) and at -6˚ (-321˚ to -52˚), respectively (b). *Hours after lights on.

Circaseptan rhythm in mortality following inoculation of P. berghei into mice. BALB/c (a) and DBA (b) mice were inoculated, data were pooled (c) and summarized by single cosinor with the fit of a 7-day period (d): P=0.014; percentage rhythm = 51. In deaths per day, the MESOR ± SE is 3.1 ± 0.6 and the amplitude is 3.2 with 95% confidence limits (CL) from 0.7 to 5.7. The acrophase (with 360˚ ≡ 168h) is at -325˚ from inoculation time, with 95% CI from -276˚ to -378˚.

Figure 12A. Top: Circadian rhythm in rodent susceptibility to P. berghei. BALB/c mice (at four/timepoint) and DBA mice (at seven/timepoint) were inoculated i.p. with 10,000 parasitized erythrocytes at one of 4 or 6 different circadian host stages, defined by standardization in light (empty bar) and darkness (dotted bar) alternating at 12-h intervals (a). Evaluation at 54% and 51% overall mortality. For the two groups, the percentage rhythm is 90 and 93, the P is 0.033 and 0.020; the MESOR (in percentage survivors) ± SE is 46.0 ± 5.2 and 47.0 ± 4.8; the amplitude (in percentage survivors) and 95% confidence limits (CL) are 30.0 (4.3-56.0) and 41.0 (11.9-71.0) and the acrophase and CL (with 360˚ ≡ 24h and 0˚ = L-on) are at -44˚ (-345˚ to -103˚) and at -6˚ (-321˚ to -52˚), respectively (b). *Hours after lights on.

Bottom: Circaseptan rhythm in mortality following inoculation of P. berghei into mice. BALB/c (a) and DBA (b) mice were inoculated, data were pooled (c) and summarized by single cosinor with the fit of a 7-day period (d): P=0.014; percentage rhythm = 51. In deaths per day, the MESOR ± SE is 3.1 ± 0.6 and the amplitude is 3.2 with 95% confidence limits (CL) from 0.7 to 5.7. The acrophase (with 360˚ ≡ 168h) is at -325˚ from inoculation time, with 95% CI from -276˚ to -378˚. © Halberg.

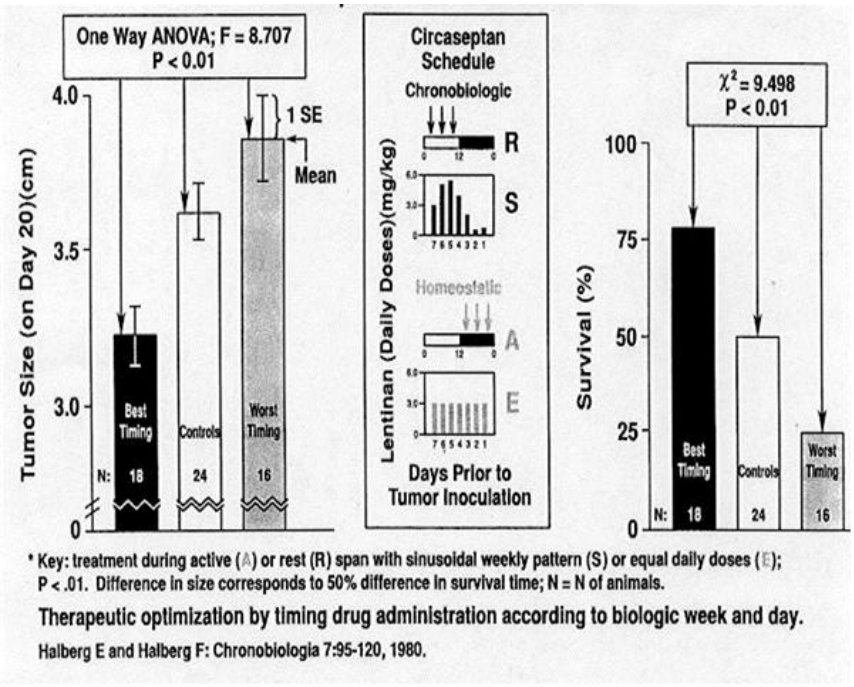


Figure 12B. Multifrequency chronotherapy. The same total dose of a drug (lentinan) as a function of its administration pattern can enhance tumor growth when given in equal doses daily at one circadian stage (homeostatically) and inhibits growth when given at another circadian stage with a sinusoidal pattern (chronotherapy). © Halberg.

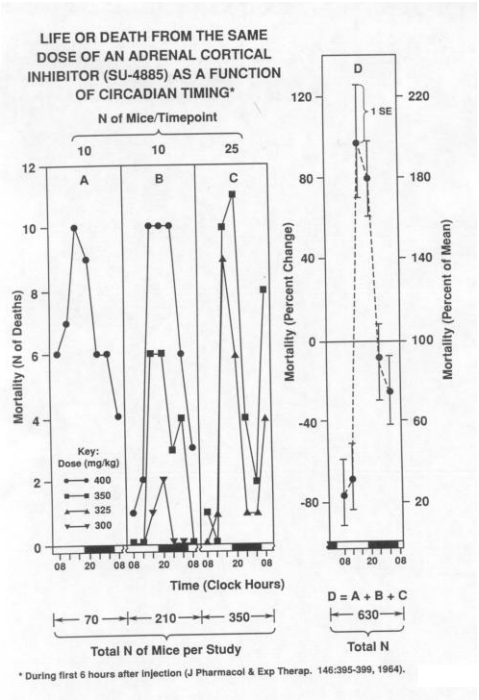
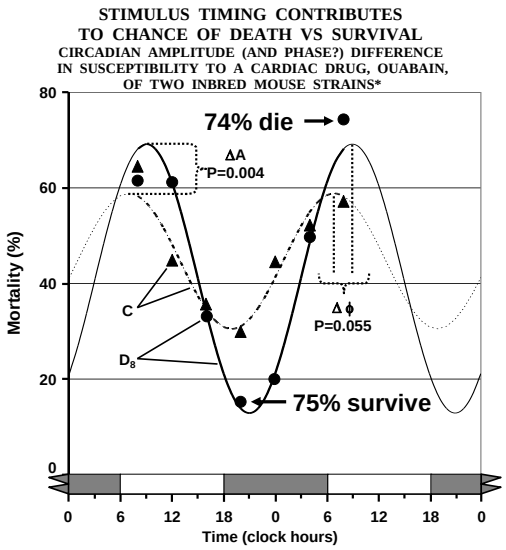


Figure 13A. Circadian susceptibility resistance cycle to SU-4885. © Halberg.



Strain	P	M	Amplitude (A)	Acrophase (ϕ**)
D_8	P < 0.001	40.0	28.1 (21.5; 34.8)	-135 (-119; -150)
C	P = 0.011	45.2	14.2 (7.3; 21.0)	-104 (- 73; -136)

*** C: Bagg albino, D_8: subline 8 of Dilute Brown strain; ouabain 0.15 or 0.5 mg/20 g of body weight, respectively. Thin lines in the graph are extrapolations of fitted cosine curves. ** In the table: 95% confidence limits in parentheses, ϕ in degrees (360^o ≡ 24 hours). M = MESOR; P from zero-A (no-rhythm) test.**
Data from F.Halberg et al., Minnesota Acad Sci Proc 1959; 27: 139-143.

Figure 13B. Circadian susceptibility resistance cycle to ouabain. © Halberg.

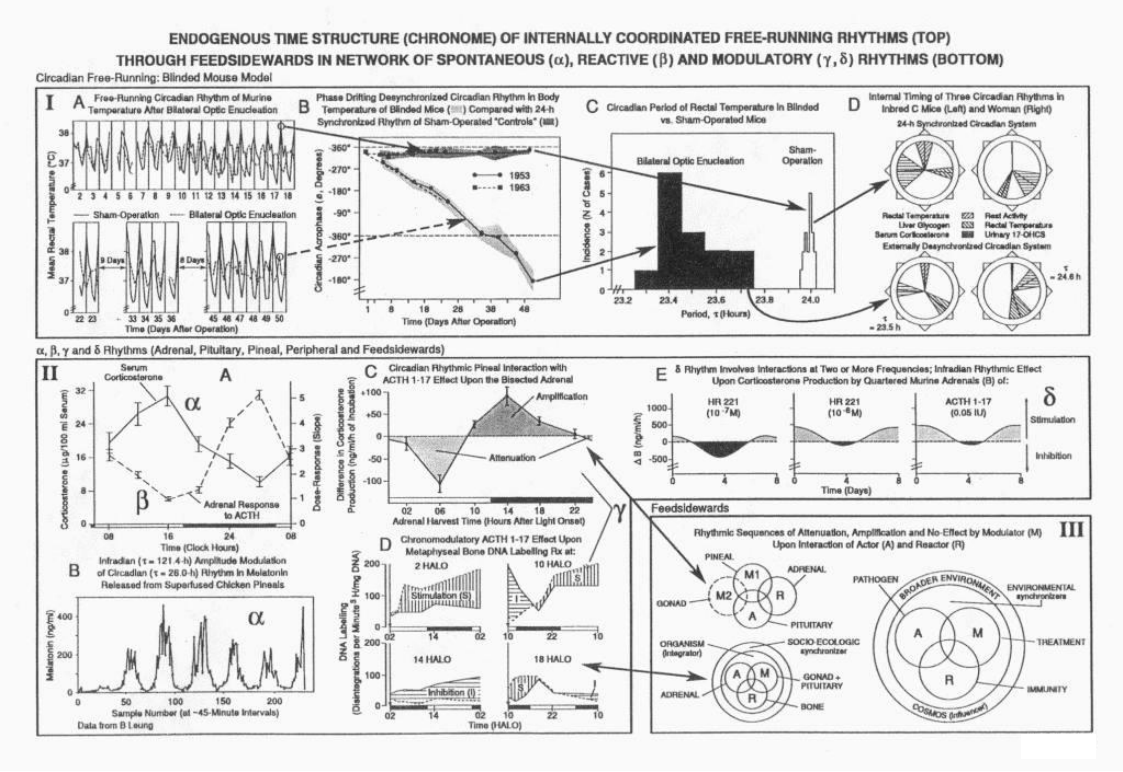


Figure 14. Top, section I: Desynchronization of circadian rhythm in core temperature of mice after blinding, seen time-macroscopically in IA, here leads, in IB, to time-microscopy with a

chronobiologic serial section showing a different time course of the core temperature acrophases, φ, with early separation of the two groups by non-overlapping 95% confidence intervals of φ in IC, to a summary of individual periodograms that form two separate distributions, and in ID to time relations among three variables in a 24-hour synchronized (top) or free-running (bottom) system (of mice, left, and of a human, right). Section II shows a spontaneous (α) rhythm in circulating corticosterone of mice in antiphase with the slope of an in vitro response rhythm to ACTH, a reactive (β) rhythm. The components of the chronome (time structure) are internally coordinated through feedsidewards in a network of rhythms that are more or less spontaneous (α), others primarily reactive (β) or modulatory at a single mapped frequency, such as a circadian (γ), IIC and IID, or at multiply mapped (δ) frequencies, IIE.

The effect of one entity (the actor) upon a second (the reactor), such as the pituitary acting upon the adrenal cortical corticosterone production may be influenced, predictably insofar as rhythmically, by a third entity such as melatonin (the modulator) at the level of the pituitary and the same melatonin may act directly upon the adrenal. Reproducible sequences of attenuation, no-effect, and amplification, the time-qualified feedsidewards, replace time-unqualified feedbacks and feedforwards (IIC to E). In sections II and III, feedsidewards include the interaction of a modulator (such as ACTH) upon an actor (such as adrenocortical corticosterone production) acting upon DNA labeling in bone (the reactor). The roles played by endocrines can and do change in various feedsidewards that replace time-unqualified feedbacks and feedforwards (see Figure 15O). Chronomolecular mapping of circadian acrophases has also begun. © Halberg.

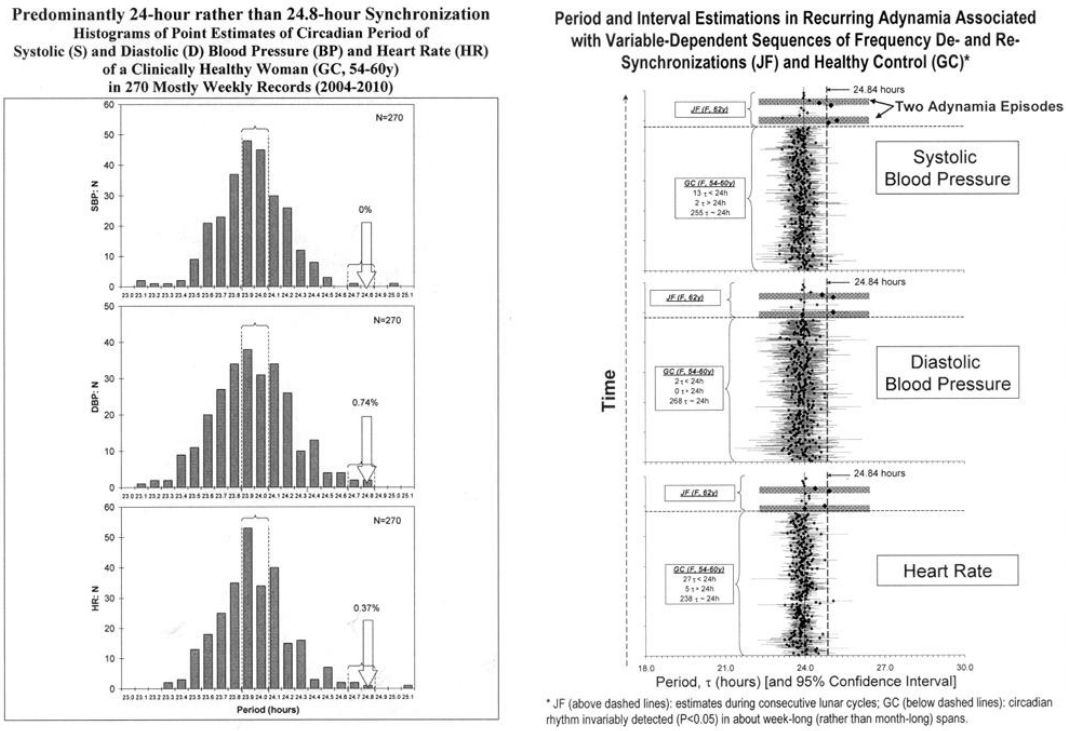
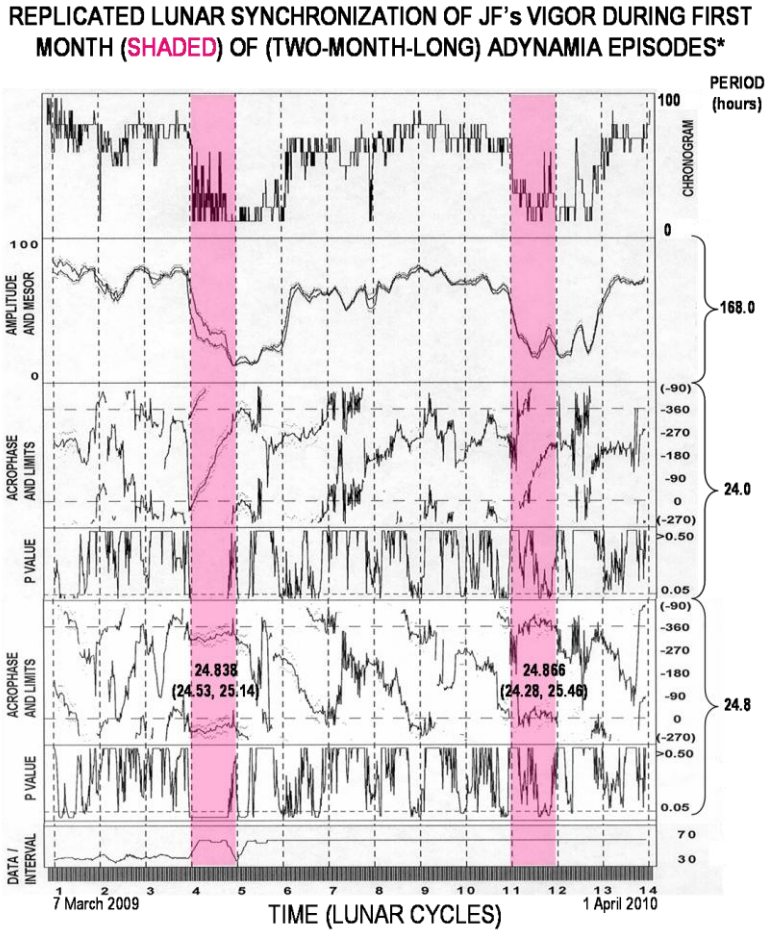


Figure 15A. In the blood pressure and heart rate of a clinically healthy woman studied at 30-minute intervals around the clock over several years, the frequency of one cycle in (a double

earth tidal average of) 24.8 hours is extremely low and was not yet detected twice in succession in the same person (GC) in this case or any other studied over the past half-century by ourselves, in health, under conditions of life on a 24-hour average schedule, information that sets the stage for the following slides on JF, a patient with a history of >20 years of twice-yearly depression, *Table 2*. © Halberg.



*Dashed vertical lines: full moons (JF reports sensitivity to the moon). N data: 2820; interval: 168 hours; increment: 12 hours.

Figure 15B. The double tidal average is seen in the first lunar month of two consecutive adynamic episodes investigated in JF – in the computer output of the nonlinearly extended cosinor – in data on self-rated vigor (top row). In the second row, the lower curve is the weekly average (MESOR) which summarizes the original data on vigor on top, more clearly revealing the twice-yearly episodes of 2-3 months, of which the first lunar month is shown by vertical pink columns. The difference between the two curves in the second row is the very small circaseptan amplitude, which increases notably during the first episode. The third row shows that, during the first month of each episode, the phase of a 24-hour cosine fit delays and is statistically significant below the dashed horizontal line indicating the 5% level (in row 4) during that month in the first episode. With the fit of a 24.8-hour cosine, the phases are more or less horizontal during the first month of each episode indicating a good fit of the double tidal period (in row 5). The numbers inserted in row 5 are from a nonlinearly extended cosinor with the CIs (95% confidence intervals) of the period given in parentheses. None of these CIs covers 24.0 h; both cover 24.8 h. © Halberg.

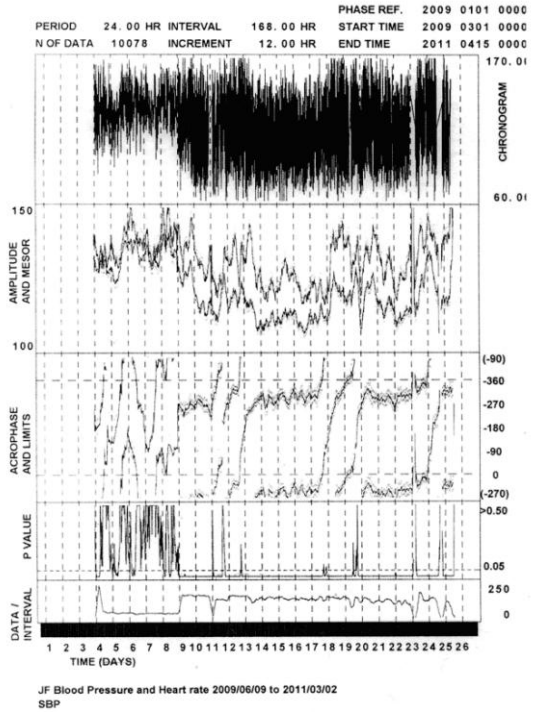


Figure 15C. Time course of a 24-hour cosine fit to JF's systolic blood pressure, revealing alternating apparent dominance of 24-hour synchronization and desynchronization. © Halberg.

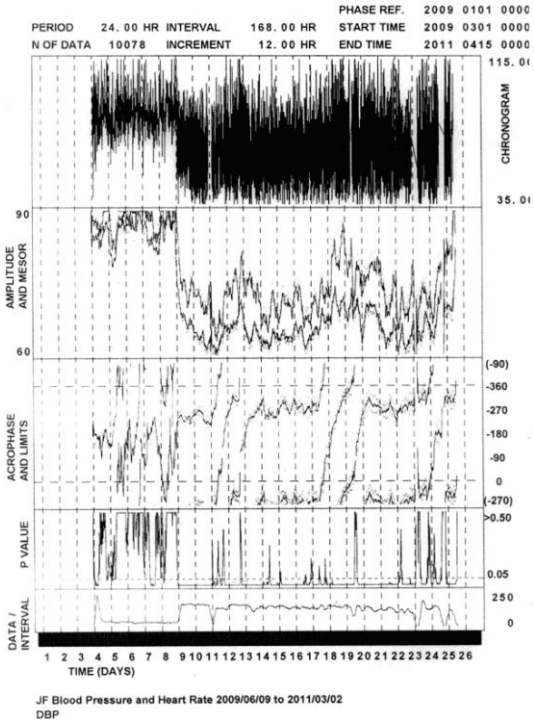


Figure 15D. Time course of a 24-hour cosine fit to JF's diastolic blood pressure, revealing alternating apparent dominance of 24-hour synchronization and desynchronization. © Halberg.

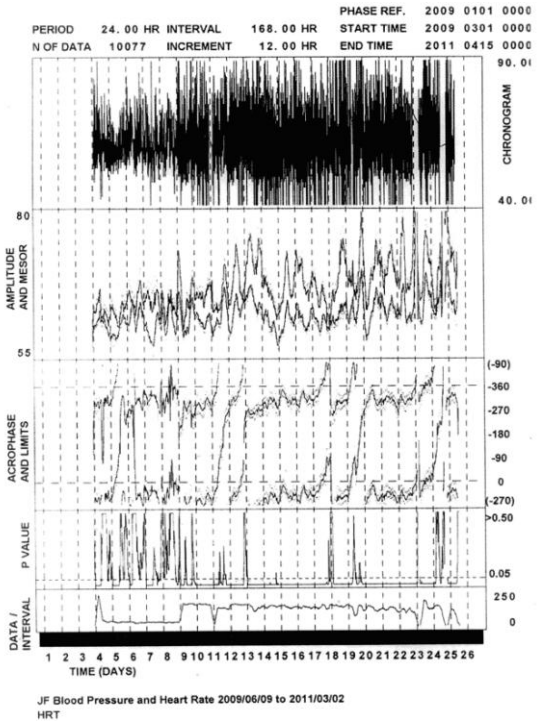


Figure 15E. Time course of a 24-hour cosine fit to JF's heart rate, revealing alternating apparent dominance of 24-hour synchronization and desynchronization. © Halberg.

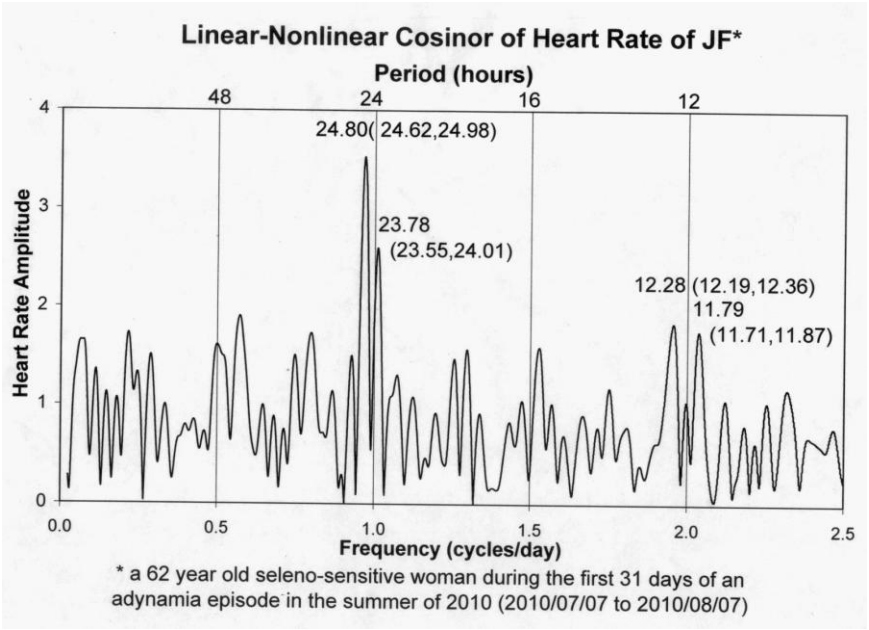


*Figure 15F*s Coexisting separate circadian τs in JF's heart rate, during an episode of depression with adynamia. A component with a 24.8-hour period dominates with a 95% confidence interval that does not overlap 24.0 hours. The second largest but numerically smaller amplitude than that of the 24.8-hour peak (of the average double tide) has a CI overlapping 24.0 hours. The more detailed time course of the heart rate's τs is seen in section G. © Halberg..

Coexisting societal-light 24.0-hour (dots) and tidal 24.8-hour (diamonds) components dominating during wellness and illness, respectively (JF, F, 62 y)

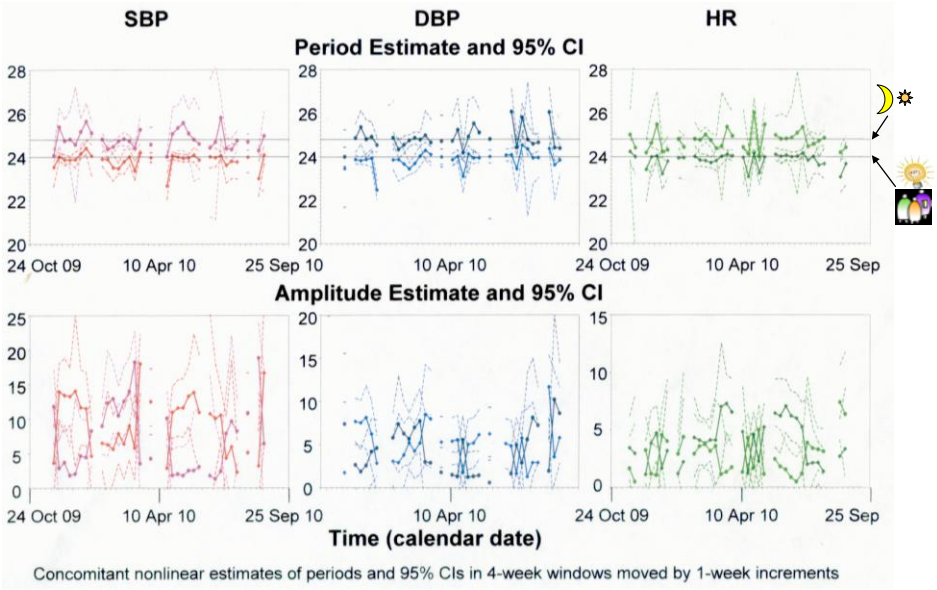
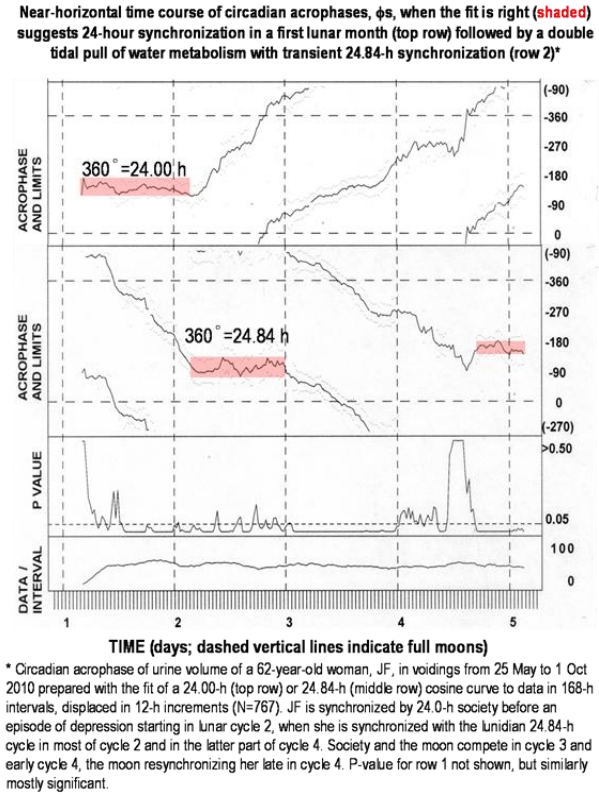


Figure 15G. Time course of two separate coexisting circadian τs in JF's circulation, alternating in (and wrangling for) dominance, as seen by the differences in their amplitudes. © Halberg.

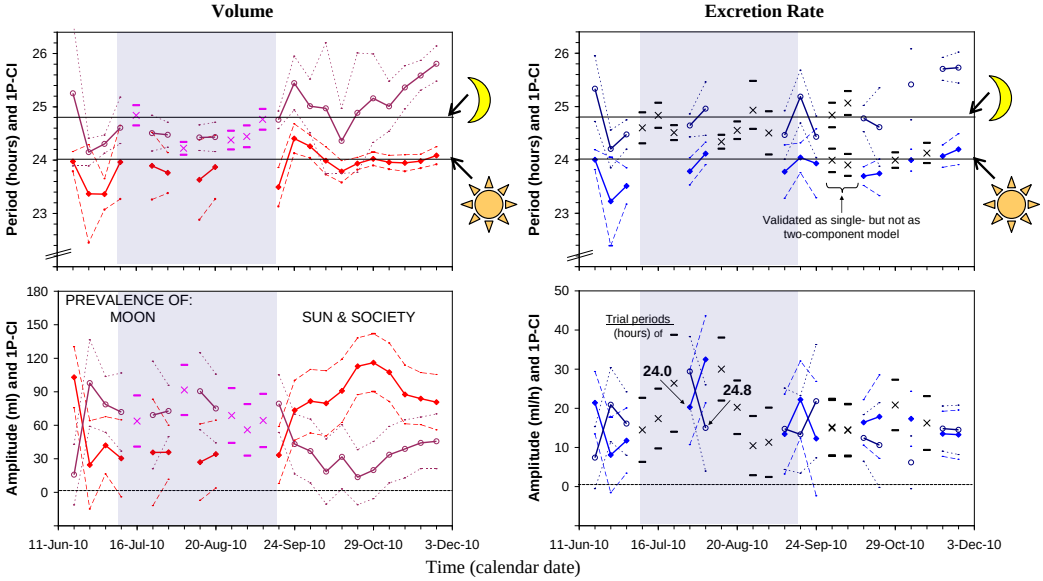


* Circadian acrophase of urine volume of a 62-year-old woman, JF, in voidings from 25 May to 1 Oct 2010 prepared with the fit of a 24.00-h (top row) or 24.84-h (middle row) cosine curve to data in 168-h intervals, displaced in 12-h increments (N=767). JF is synchronized by 24.0-h society before an episode of depression starting in lunar cycle 2, when she is synchronized with the lunidian 24.84-h cycle in most of cycle 2 and in the latter part of cycle 4. Society and the moon compete in cycle 3 and early cycle 4, the moon resynchronizing her late in cycle 4. P-value for row 1 not shown, but similarly mostly significant.

Figure 15H. Chronobiologic serial sections of JF's urine volume, with the fit of a 24-h cosine in the top row and of a 24.8-hour cosine curve in the second row. The top row suggests 24-h

synchrony during wellness in a first lunar cycle and a delaying time course, i.e., a lengthening of period, τ, during the remainder of the time of adynamic depression indicating desynchronization from society's 24-hour schedule. In the second row, during the first lunar month, the phase advances because the 24-h period is shorter than the 24.8-hour τ fitted in this row. This fit is appropriate during the second lunar month when depression starts, as seen by a horizontal time course, and again near the end of the record, when the 24.8-hour fit again has a horizontal time course of phases. After the second lunar month, wrangling follows with a shortening of the τ suggested by an again-diagonal time course of advancing phases, ϕ, until the ϕ again becomes horizontal, i.e., the fitted 24.8-h τ is mostly dominant. During lunar months 2-5, behavioral depression occurs, during which the ϕ is pulled with alternating dominance of the 24.8-hour and 24.0-hour periods, as is also the case in other variables in the first completely investigated episode in section J below, in keeping with the possibility of wrangling by the tides and society, the former dominating usually during the first month of depression and regaining control again during another subspan of a depressive episode. © 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).

Figure 15I. Coexisting circadian (~24.0-h and longer) urine volume (left, top) and excretion rate (right, top) dominate in alternation, as seen from their amplitudes (bottom). © Halberg.

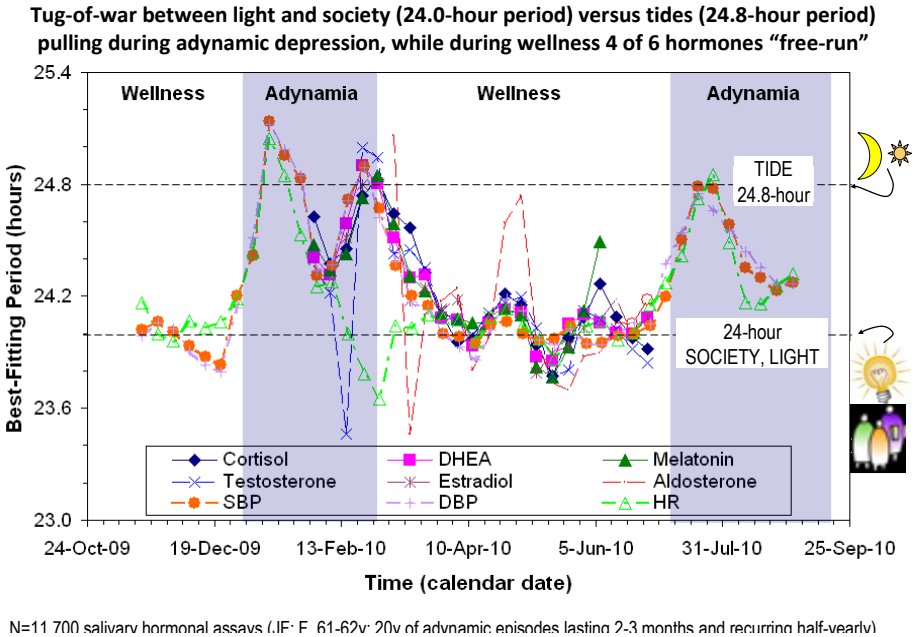


Figure 15J. Wrangling between the tides (the gravitational pulls of moon/sun) on the one hand and society on the other hand in JF's endocrines and in her circulation, with the pull of the tides lengthening the dominant τ during spans of depression shaded as vertical blue-shaded columns. Note, for more than one variable, two separate dominances of 24.8 hours by the periods plotted during the same first completely investigated episode, the first a clear overshoot. © Halberg.

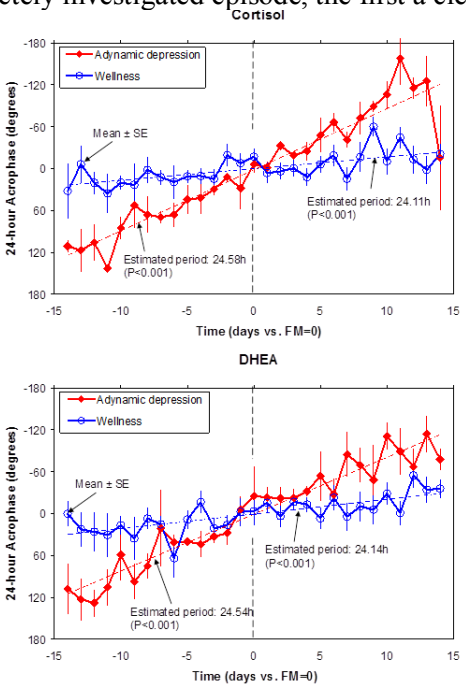


Figure 15K. Diagonal (desynchronized) time course of JF's phases in salivary cortisol and DHEA during depression (red) is prominent, yet slightly present during wellness as well (blue) when the period still differs (is free-running) from precisely 24.00 hours (P<0.001). © Halberg.

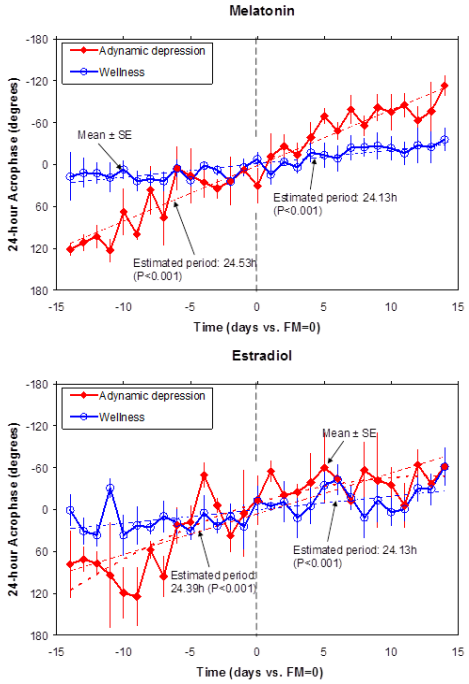


Figure 15L. Diagonal (desynchronized) time course of JF's phases in salivary melatonin and estradiol during depression (red) is much less prominent yet slightly present during wellness as well (blue), with a period differing (free-running) from precisely 24.00 hours (P<0.001). © Halberg.

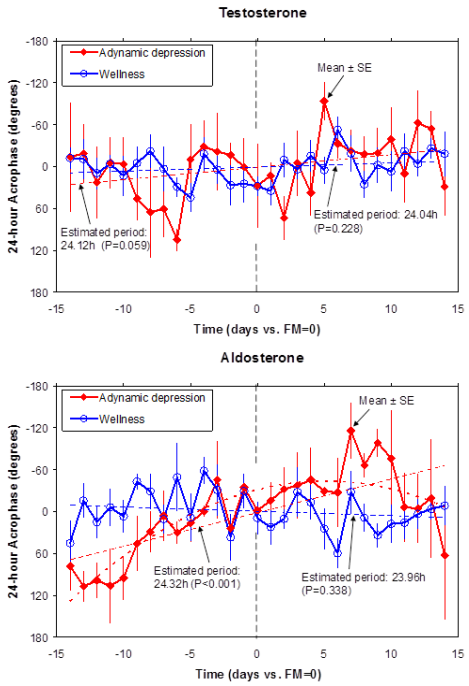


Figure 15M. Diagonal (desynchronized) time course of JF's phases in testosterone and aldosterone, prominently present during depression (red), is not seen in testosterone and aldosterone during wellness (blue), presumably because of selective synchronization by twice-daily spironolactone treatment. © Halberg.

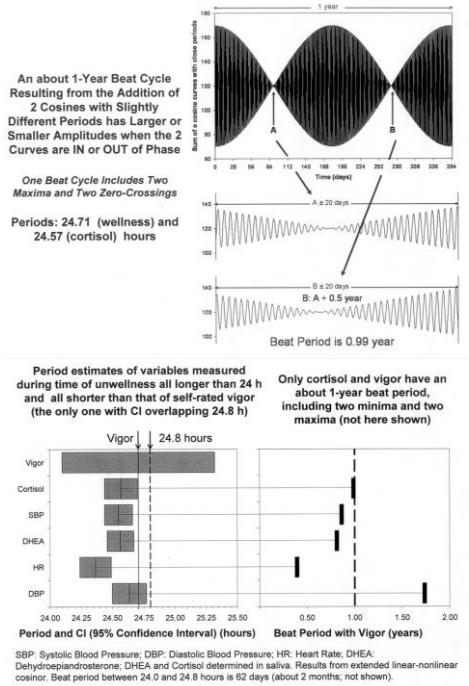


Figure 15N. Abstract visualization of a hypothetical factor underlying vigor/wellness beating with some other factor (cortisol?). If the twice-yearly episodes of adynamia in JF should come about as a beat of neighboring τs, the nearest beat τ to 1 y in the data that happened to be available at the time of this analysis involves cortisol, and this abstract model (above) was thus in keeping with the twice-yearly recurrence (in section B) of adynamia (a prominent symptom of adrenocortical insufficiency). © Halberg.

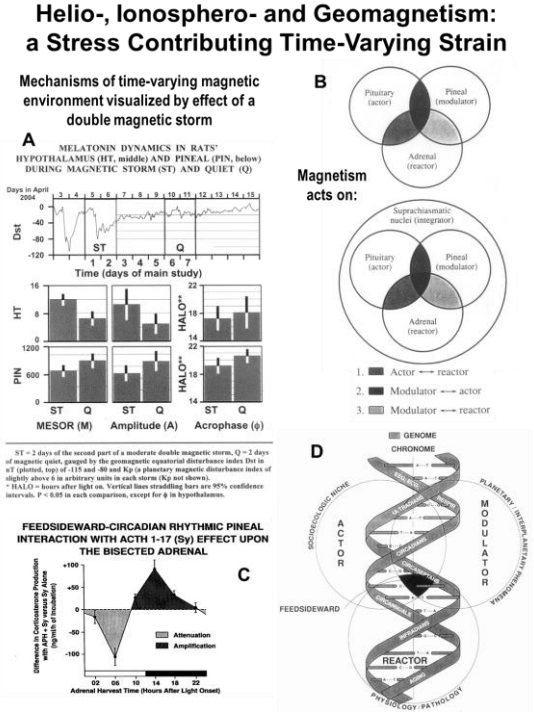


Figure 15O. JF reports that she is sensitive to the moon and to helio- and geomagnetism. The

double tidal period and its wrangling with the societal schedules are in keeping with her claim. Underlying mechanisms can be explored by the following survey in the laboratory (170):
(A) Observations on the equatorial geomagnetic index Dst (top), on the hypothalamus, Ht (middle) that may be activated via the storm directly and/or via the pineal, Pin (bottom). Concerning an effect of the storm (top) upon the neuroendocrine network (below), also showing adrenocortical involvement. These unplanned observations on rats can be aligned with observations of a decreased human urinary excretion of melatonin during magnetic storms in keeping with a damping of pineal function, including its dynamics, gauged by the lower circadian amplitude during the storm. This "experiment of nature" offers a putative mechanism that cannot be dissected in vivo in the pineal and/or hypothalamus of humans.
(B) Lack of effect, attenuation, or amplification by aqueous pineal homogenate (APH) of corticosterone production by bisected adrenals in response to a synthetic ACTH 1-17, Synchrodyn (Sy). When magnetic storms reach an organism, their effect will depend upon the network's stage at exposure times, e.g., in the case of a double storm shown in A.
(C) Results such as those in A and B are summarized in C (top). The second row from the top in A illustrates the effect of a double magnetic storm on circadian amplitudes and acrophases in the suprachiasmatic nuclei (SCN) of the hypothalamus and the third row upon the circadian characteristics of the pineal. The consistent findings after SCN removal are changes in circadian amplitude and/or acrophase, and these are consistent with those in A.
(D) Chronomodulation: on the right, a modulator, representing magnetic planetary and interplanetary solar and galactic factors (their effect on geomagnetics is shown in A) are conceived as normally modulating or, as storms, altering the (socio-)ecological conditions in the habitat, e.g. the synchronizing effect of the lighting regimen (the actor in the animal room), acting upon the organismic hypothalamic-pineal-adrenocortical-vascular network. © Halberg.

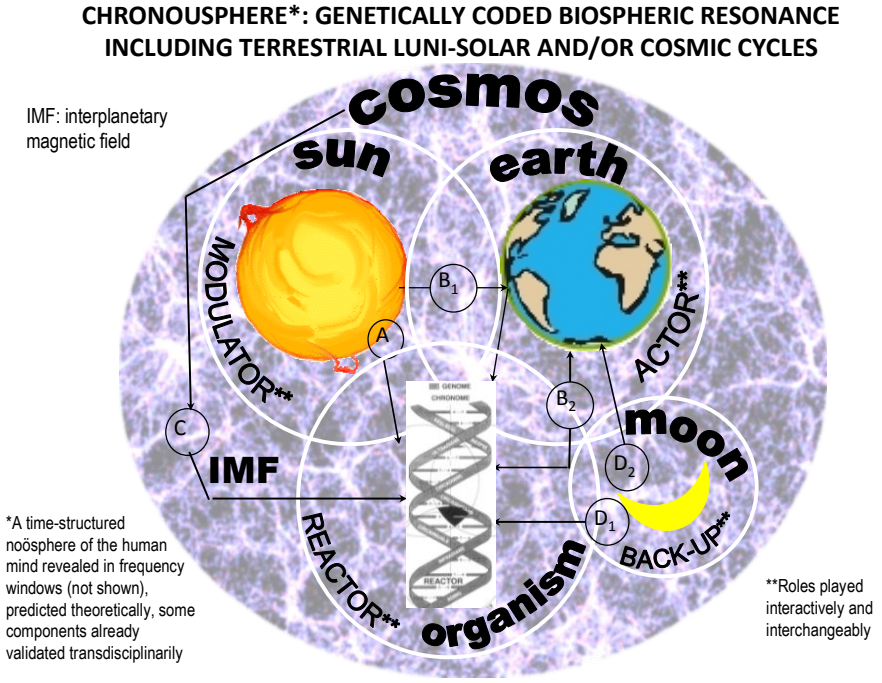


Figure 15P. That the pull of the tides influences the human circulation, as found by Miroslav Mikulecky for the case of his arrhythmias (133) is supported by the repeated detection of the average double tidal period in JF and may act on melatonin in both the pineal and the hypothalamus, in keeping with data on the rat for the case of a magnetic storm. © Halberg.

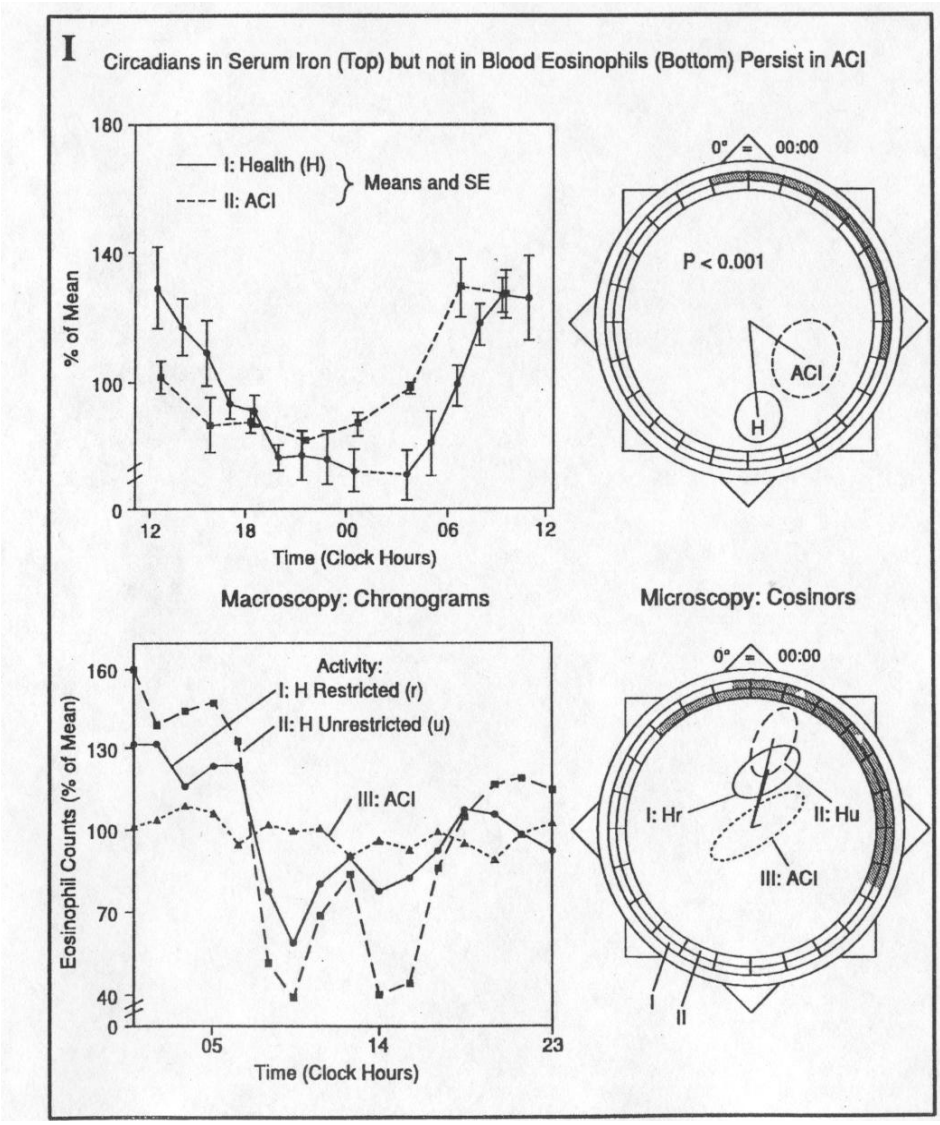


Figure 16. Chronobiologic self-experimentation extended to groups of medical students and staff served to find that the adrenal glands are an important source of circadian rhythmicity in the circulating eosinophil count. For instance, a circadian component of variation could not be demonstrated for eosinophil counts of patients with adrenocortical insufficiency (bottom), whereas in healthy people with either restricted or unrestricted activity, this rhythmicity was not only demonstrable, but also amplified by enhanced motor activity. Whereas for patients with Addison's disease a circadian rhythm in eosinophil counts could not be statistically validated, circadians persisted, albeit altered, for the case of serum iron ($P < 0.001$) (top). As subsequently by the case of bilateral, histologically validated ablations of the suprachiasmatic nuclei, some rhythms persist; others may be altered but are not lost in remove-and-replace approaches studied thus far. © Halberg.

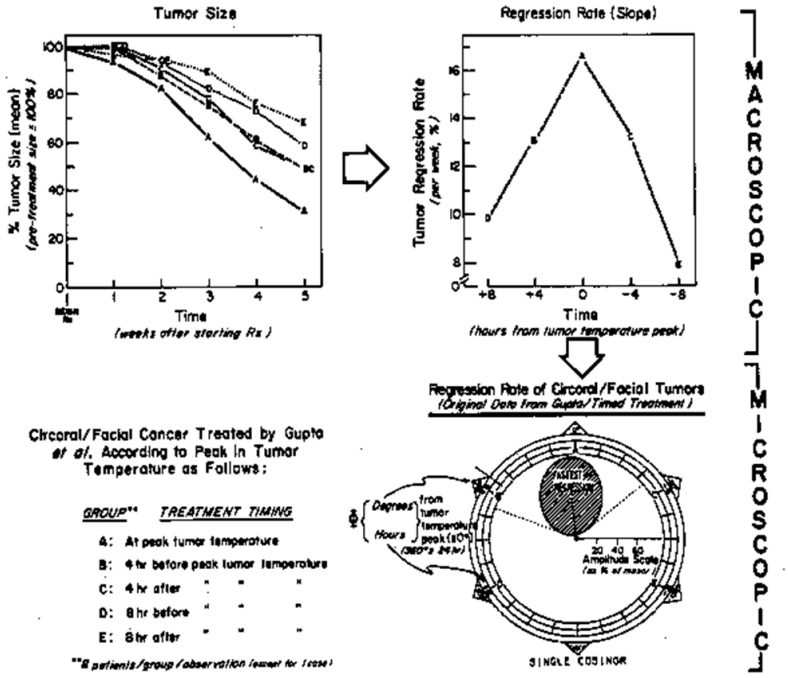


Figure 17A. Tumor regression rate is circadian stage-dependent in response to X-irradiation. © Halberg.

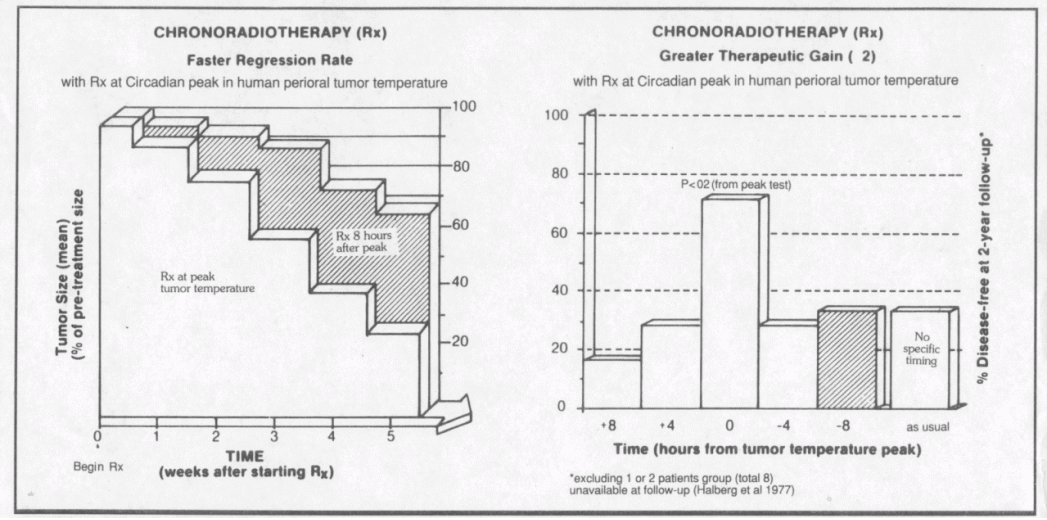


Figure 17B. Treatment timing at peak tumor temperature leads to faster tumor regression (left) and to more than doubling of the 24-month disease-free survival rate (0 on abscissa, right), as compared to reference groups treated 4 or 8 hours before or after the tumor temperature peak (+8, +4, -4, -8 on abscissa, right) or "as usual" (last column, right). Studies implemented by B.D. Gupta and Akhil Deka, designed during a PL-480 program sponsored by the USA (26). © Halberg.

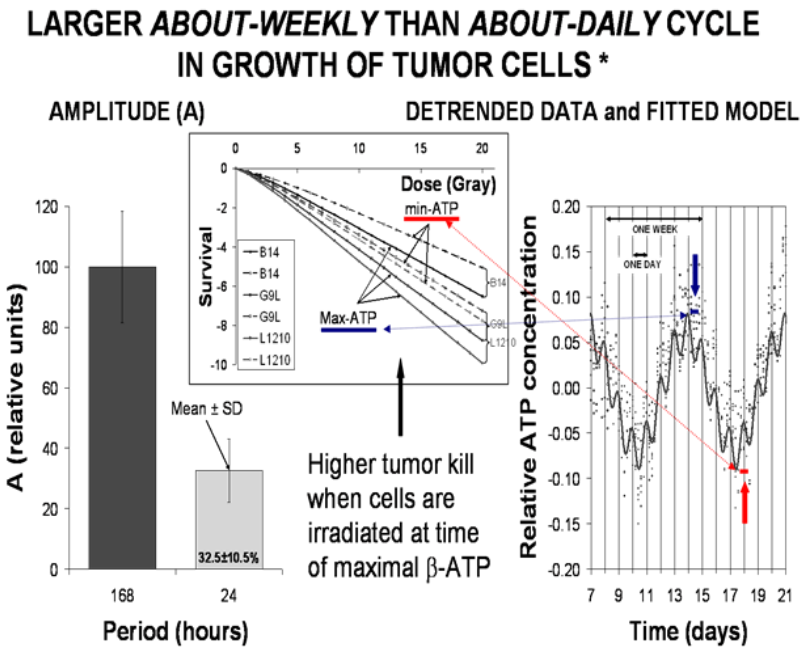


Figure 18. Circaseptan optimization in a 9L glioma rat tumor model may be even more important than circadian chronotherapy (see also *Figure 12B*). © Halberg.

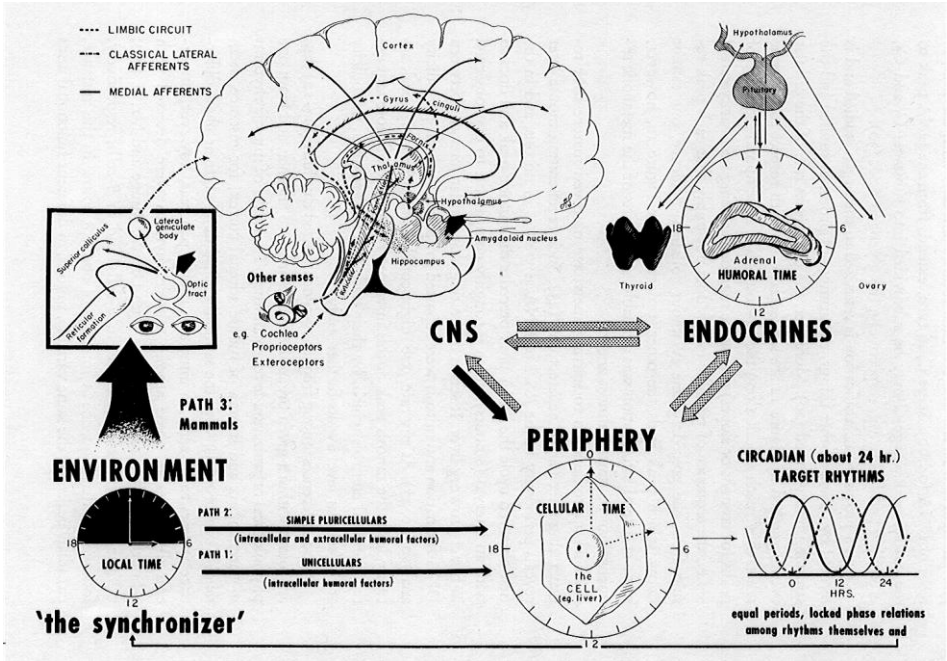


Figure 19. Sketch of factors and pathways known or hypothesized to participate in frequency synchronization *among* circadian rhythms themselves, as well as in synchronization *between* rhythm(s) and environmental synchronizer(s). Emphasis upon the cell as a documented source of rhythmicity by 1960 (40, 70, 76). © Halberg.

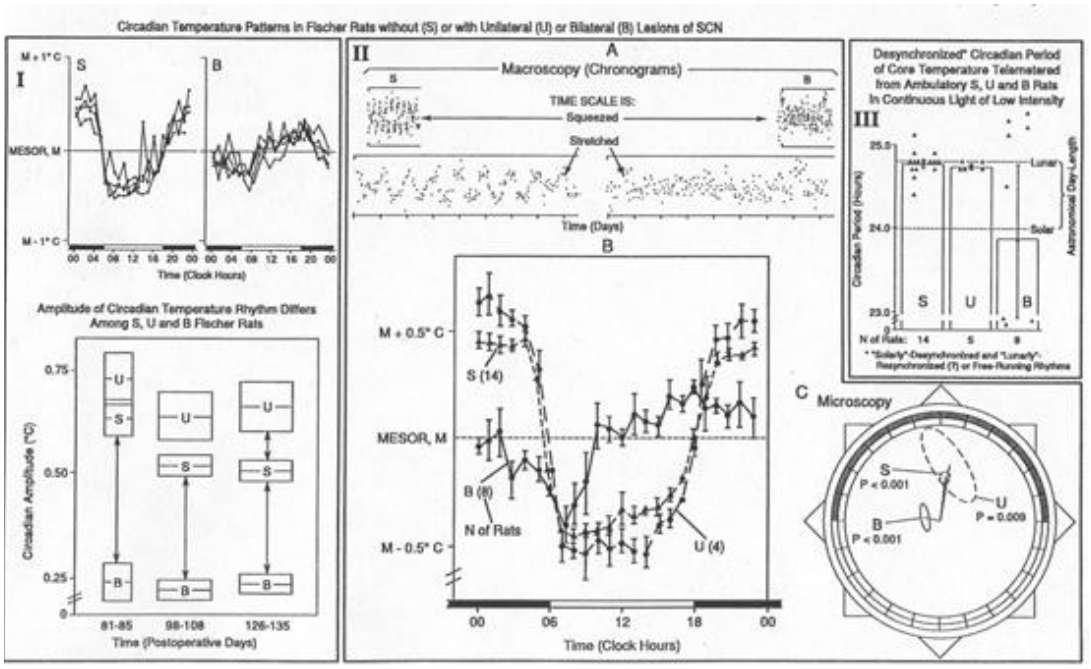


Figure 20A. Much controversy has revolved around the circadian rhythm alteration after lesioning of the suprachiasmatic nuclei (SCN). Several investigators have claimed, without cosinor analyses, that all circadian rhythms are obliterated after bilateral lesioning of the SCN; others including ourselves have found, with cosinor analyses, a rhythm alteration to a differing extent and in different direction (amplification as well as damping) for different variables rather than an overall obliteration after such intervention. Evidence supporting the persistence of rhythms after bilateral lesioning of the SCN illustrates the merits of chronobiometric analyses to obtain a valid interpretation of the data. This figure shows the circadian temperature patterns in Fischer rats, without or with unilateral or bilateral lesions of the SCN. A visual inspection of the original core temperature data (IIA) may erroneously convey the impression that rhythmicity clearly seen in the series on the left is abolished in the series on the right. The use of simple chronobiologic techniques such as a plexogram (that is, the stacking of the data over an idealized anticipated cycle of 24 hours) shows that there is a persisting circadian pattern, albeit an altered one, with a reduced amplitude and an advanced phase, IIB and C. This is also shown in curves obtained from several different animals (IC and D). Whereas the circadian amplitude of core temperature of rats with a histologically validated bilateral lesioning of the SCN is much reduced, it is noteworthy that in rats with a unilateral lesion of the SCN, the amplitude is actually larger than that of sham-operated rats.

Evidence supporting the influence of planetary-interplanetary phenomena is provided by the fact that sham-operated rats and rats with a unilateral lesion of the SCN kept in continuous light of low intensity have a circadian period of core temperature that is desynchronized from 24 hours, with an average period close to the "lunar" day (or rather one of the earth's double tidal periods); this is not the case for rats with a bilateral lesioning of the SCN which can have either a shortened or lengthened circadian period (III). © Halberg.

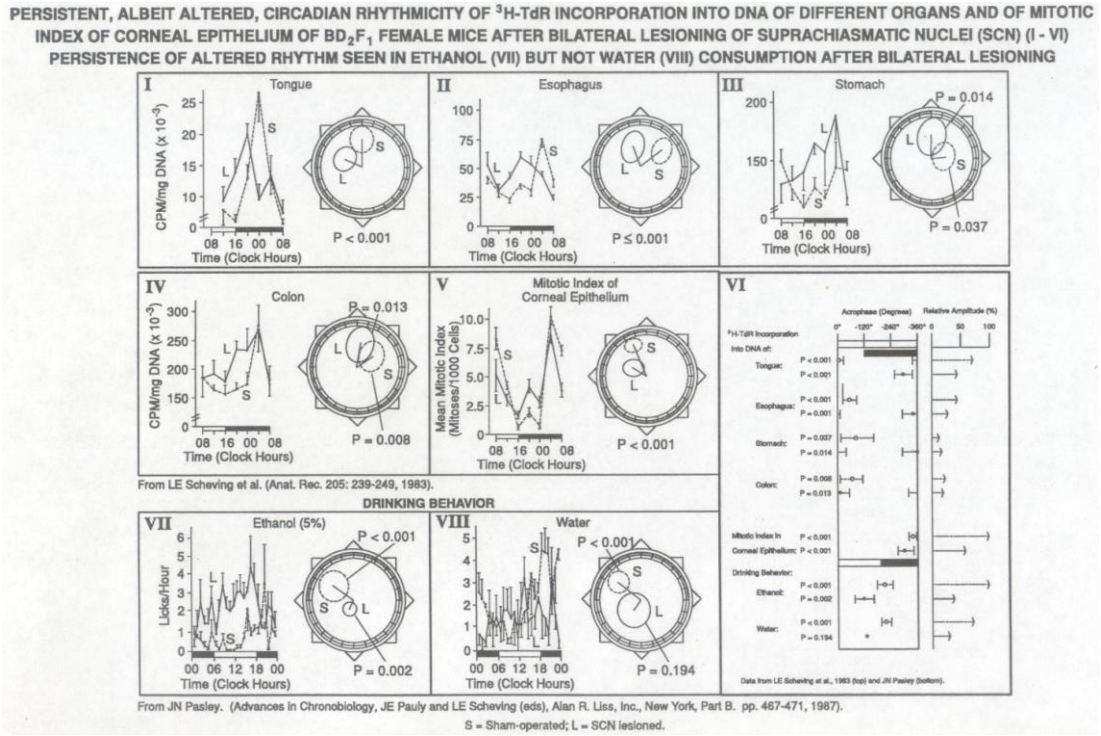


Figure 20B. Persistence of the circadian rhythmicity of the ^{3}H-TdR incorporation into DNA of different organs and of the mitotic index of the corneal epithelium of BD_2F_1 female mice after bilateral lesioning of the SCN has also been extensively demonstrated by Scheving (I-VI) (81) and Pasley (VI and VII) (171). For animals with a bilateral lesion of the SCN, a cosinor on Pasley's data could not validate a circadian rhythm in the drinking of water, but demonstrated it (P=0.002) for the drinking of 5% ethanol (VI and VII). The SCN is not the sole or primary pacemaker of the entire circadian system. © Halberg.

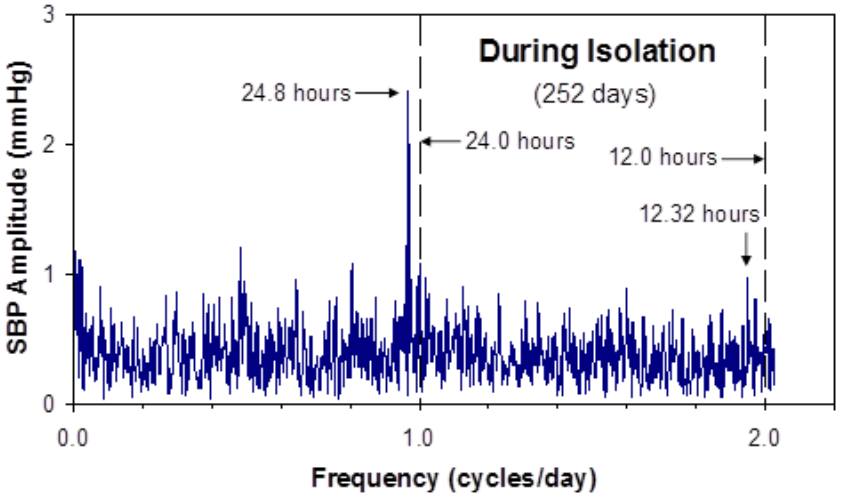


Figure 21. During the longest span of comfortable isolation from a 24-h schedule of a healthy young woman in a special underground laboratory, but not before or thereafter, a period of 24.8 h dominantly characterizes her blood circulation (among other peaklets also resolved) upon meta-analysis of original data as a whole (globally) and in serial sections (locally). © Halberg.

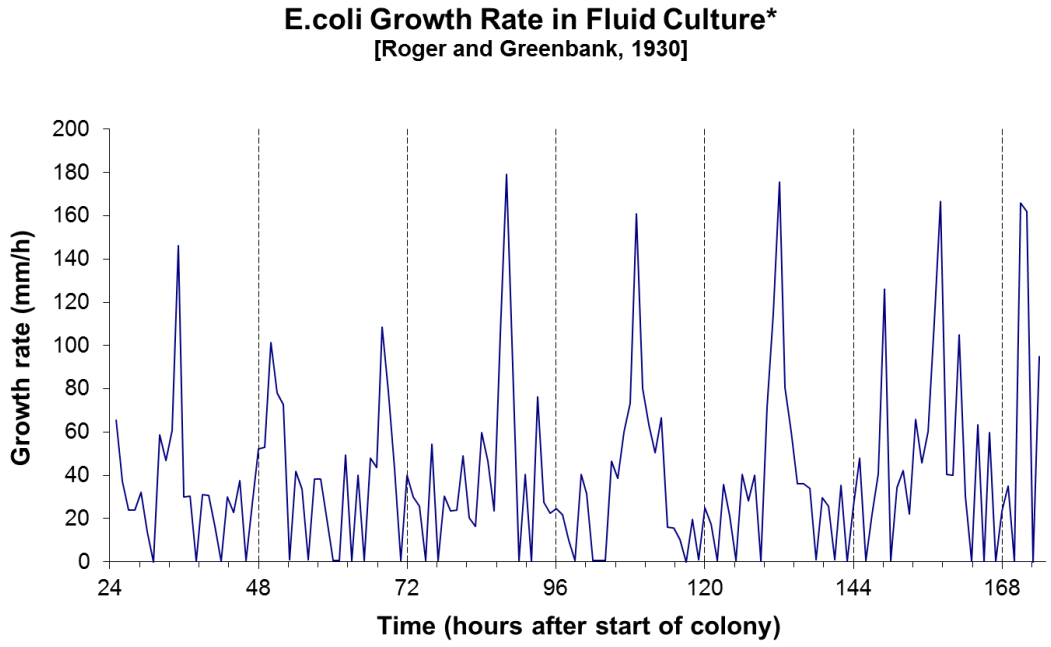


Figure 22A. Timeplot of the 1930 data of Rogers and Greenbank, a noted bacteriologist described by a Cosmos Club (Washington, DC) Vignette of December 1967 as "the bright star in the [US Department of Agriculture] scientific horizon before World War II". In 1961, the data on growth rate (actually colony advance) of *E. coli* in a spiral glass tube, assessed at hourly intervals for slightly over 6 days, were taken off the graph published by Rogers and Greenbank in 1930. Some regularity in the time series is apparent from the spikes in colony growth occurring at intervals shorter than 24 h, as seen by reference to the vertical dashed lines drawn at daily intervals, yet eyeballing can hardly serve for an estimate of a period and certainly forestalls any evaluation of uncertainties. Rogers and Greenbank wrote: "Fig. 1, which is representative of a number of experiments, shows that there is a considerable degree of periodicity to the alternation of rapid and slow growth. In considering this graph, it should be kept in mind that the curve represents not extent of growth, but rate of advance of growth for definite time periods. The number of bacteria in the different periods could not be determined." © Halberg.

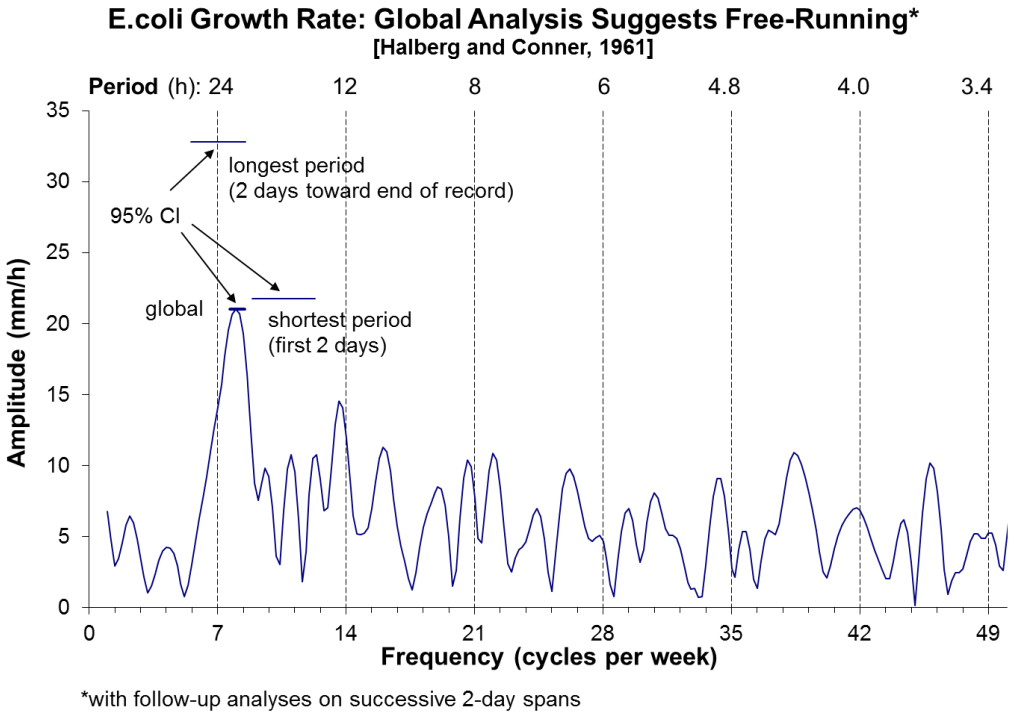
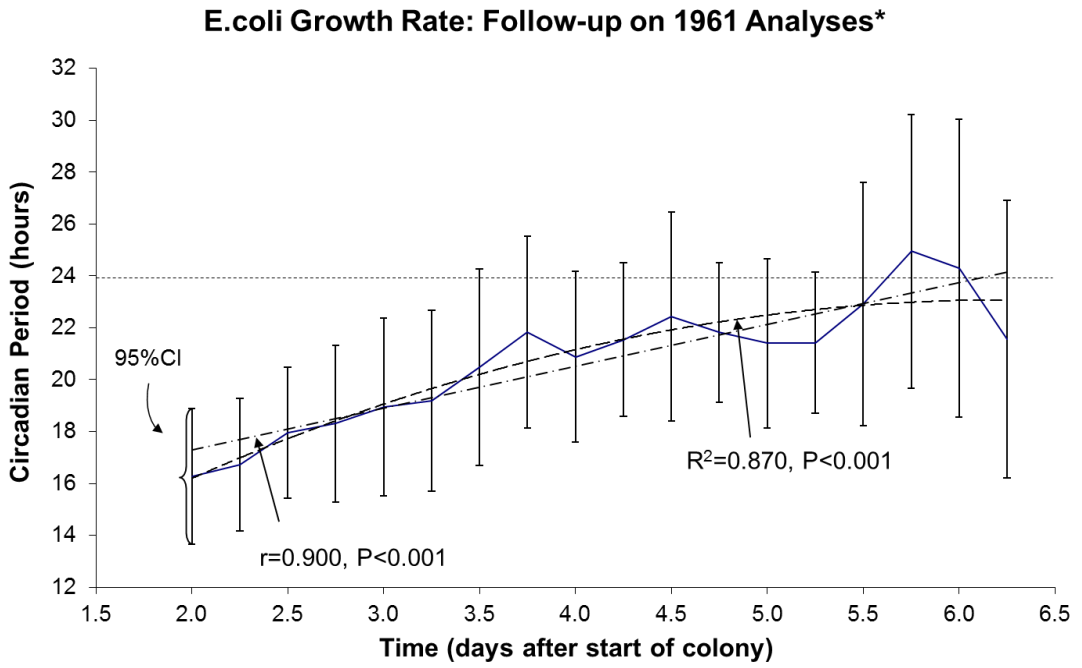
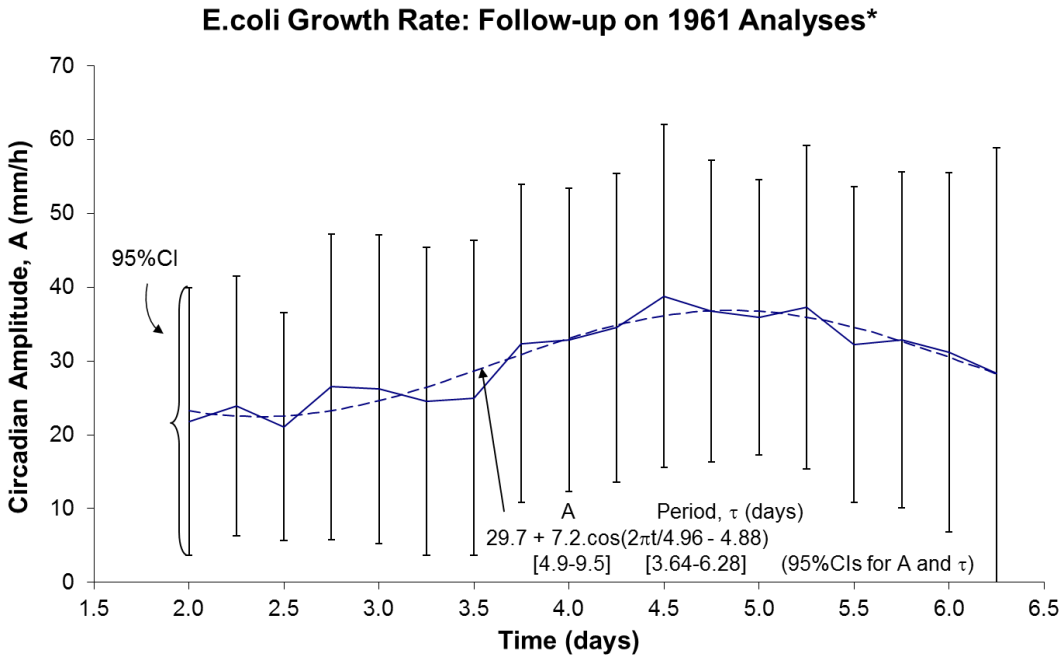


Figure 22B. By 1961, Rogers' data on growth rate of *E. coli* (A) had been analyzed by a global periodogram and power spectra to find what the naked eye may miss, i.e. what was then interpreted as a free-running circadian rhythm, with a period of about 20.75 h by Halberg and Conner (87). An infradian modulation was subsequently reported. Herein, a result of linear-nonlinear rhythmometry summarizes period estimates for 2-day sections as well as for all data with their uncertainties. The spectral peak at a frequency slightly higher than 7 cycles per week (or 1 cycle per day) confirms the visual impression of the presence of a circadian variation with a period slightly shorter than 24 h, presumably free-running. This about 21-h component accounts for 14.4% of the overall variance and is found to be statistically significant by cosinor ($P < 0.001$). Nonlinearly, the period is resolved as averaging 20.09 h (95% CI extending from 19.8-21.9 h), as shown by the horizontal bar above the spectral peak. The peak's amplitude averages 52.6% of the MESOR (chronome-adjusted mean), with a 95% CI extending from 19.4% to 85.7%, not overlapping zero (thereby rejecting the assumption of no rhythm). Additional nonlinear analyses applied to a moving 2-day interval (nonlinear chronomic serial section) indicate that this period is not fixed (C). The 95% Cls of the shortest and longest periods are also shown as horizontal bars drawn at the corresponding amplitudes. © Halberg.



*First value at 25 hours after start of colony; results of analyses assigned to midpoint of 2-day interval moved progressively by 6 hours throughout the record.

Figure 22C. Periods and corresponding 95% CIs characterizing the data shown in *Figure 22A* are here estimated for intervals of 2 days progressively moved throughout the time series by 6 h. An interval of 2 days was selected to have at least one replication to secure a more reliable estimate of the period while also allowing the investigation of any change in period length with time. Separate, non-overlapping 1-day intervals analyzed similarly yield acceptable similar estimates. The period is seen to lengthen as a function of time. As a first approximation, the dash-dotted line is in keeping with a linear increase. Being only of the order of about 18 h at the beginning of the series, it approaches 24 h by the end of the first week of monitoring. With the qualification that consecutive estimates are not independent, the lengthening of the period has an ordering $P < 0.001$ ($r = 0.900$). The fit of a second-order polynomial (solid line) suggests that the period levels off. In this model, the quadratic term significantly reduces the residual variance (ordering $P < 0.02$) beyond the linear term. The results could be interpreted as an originally free-running circadian component that may be pulled by (if not become synchronized with) the 24-h day, but there is a possible alternative, shown in D. © Halberg.



*First value at 25 hours after start of colony; results of analyses assigned to midpoint of 2-day interval moved progressively by 6 hours throughout the record.

Figure 22D. Amplitude estimates and 95% CIs corresponding to the changing periods (in C) are shown herein. With the same qualification that consecutive amplitude estimates are not independent, further liner-nonlinear analyses of the amplitude sequence indicate the presence of an infradian component with a period of about 5 days (dashed curve). The "circadian" amplitude is quite large (of the order of 50% of the MESOR), being larger in the middle of the series than at the start. The change in amplitude could be in keeping with a synchronization of the originally free-running component to a 24-h cycle, but in that case there should have been a more or less continuous increase until the end of the record. Results from the nonlinear analysis are in keeping with the alternative hypothesis of an infradian modulation of the circadian amplitude with a period of 4.96 days (95% CI: 3.64-6.28 days). It should be noted that the data were collected under presumably constant conditions, except for the hourly illumination of the colony for taking the measurements. In his nineties, Lore Rogers (the senior author) first wrote in response to an inquiry that he could not recall the conditions of the study. Later he wrote to report that his technician and co-author G.R. Greenbank (in Florida) had sent him a Christmas card. Rogers subsequently learned from Greenbank about the lack of any known external 24- or 20.75-h cycle (the latter the average cycle length in a global analysis). © Halberg.

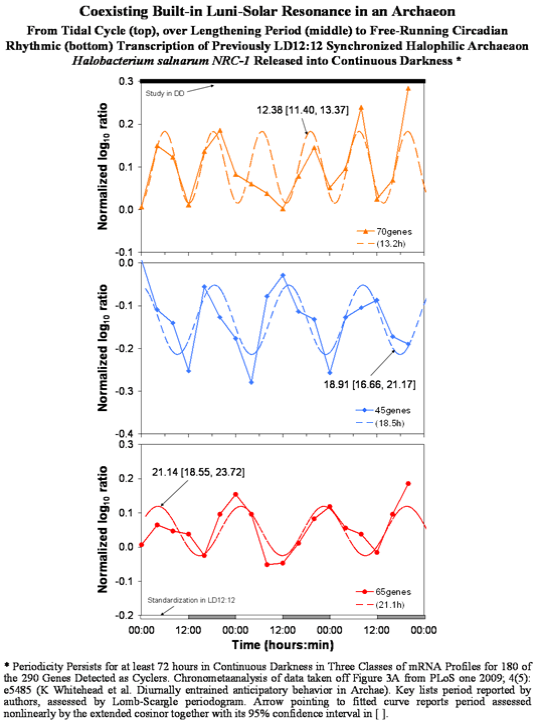


Figure 23. Assessment by the extended cosinor of periods and their 95% confidence intervals of three classes of mRNA profiles for 180 of the 290 genes detected as cyclers by Whitehead K. et al. (Diurnally entrained anticipatory behavior in Archaea. PLoS ONE 4[5]: e5485. doi:10.1371/journal.pone.0005485) in Archae kept for at least 72 hours in continuous darkness. © Halberg.

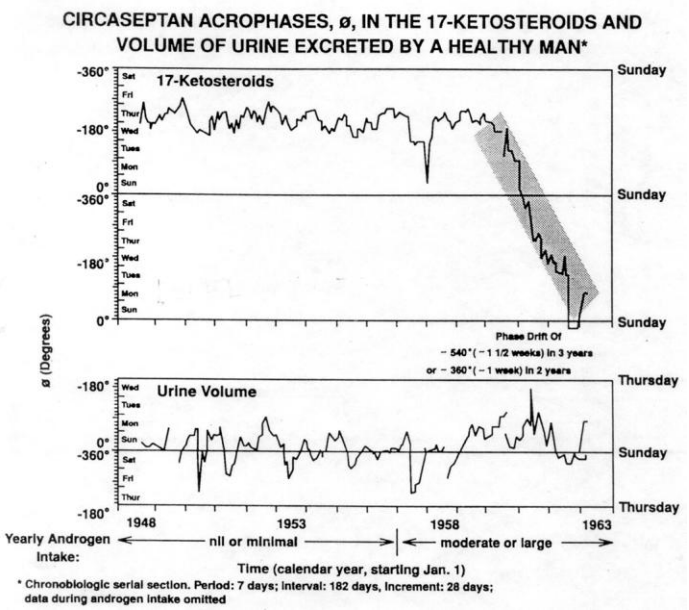


Figure 24. Circaseptan acrophases, ϕ, in the 17-ketosteroids (top) and volume of urine excreted by a healthy man, CH (see legends to *Figures 52D* and *52E*). © Halberg.

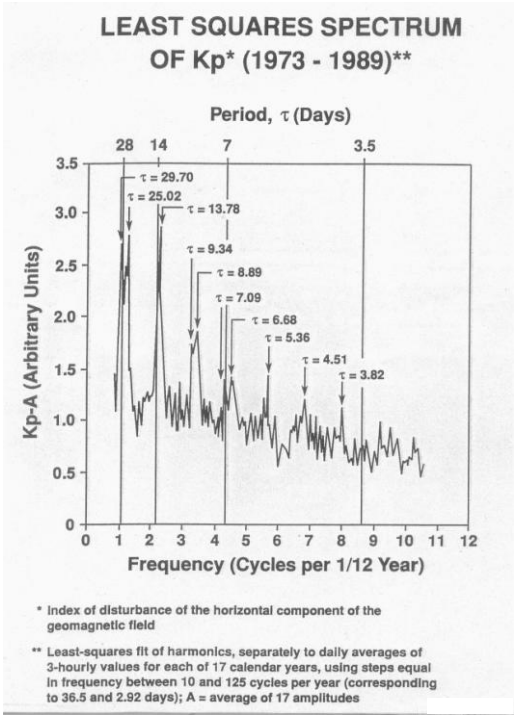


Figure 25A. Least-squares spectrum of the geomagnetic index (Kp) recorded every 3 hours for 57 years between 1932 and 1990, obtained by a population-mean cosinor spectrum, summarizing results over consecutive years. Large-amplitude peaks at periods of about but not exactly 28 days, 14 days and 7 days can readily be seen. Although the about-28-day component has long been associated with the relative motion of the moon around the earth, when it comes to geomagnetism, the about-27-day rotation of the sun around its axis has to be considered as a major source of variability in the circatrigintan range. The finding of this natural near-week of 6.68 days, and other near-weeks (*Figure 25B*), provided an environmental coperiodism of the societal week © Halberg.

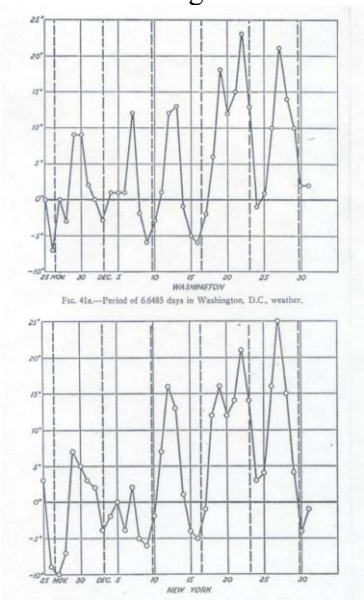


FIG. 41a.—Period of 6.6485 days in Washington, D.C., weather.

Figure 25B. "We discovered a well-marked period … of 6.6456 days (later improved to 6.6485 days) and also the half of it in the weather of New York and Washington." (Abbot CG. Solar variation and weather, a summary of the evidence, completely illustrated and documented. Washington DC: Smithsonian Miscellaneous Collections 146, No. 3 [Publ. 4545]; 1963; p. 47. *Figure 41* on p. 50.)

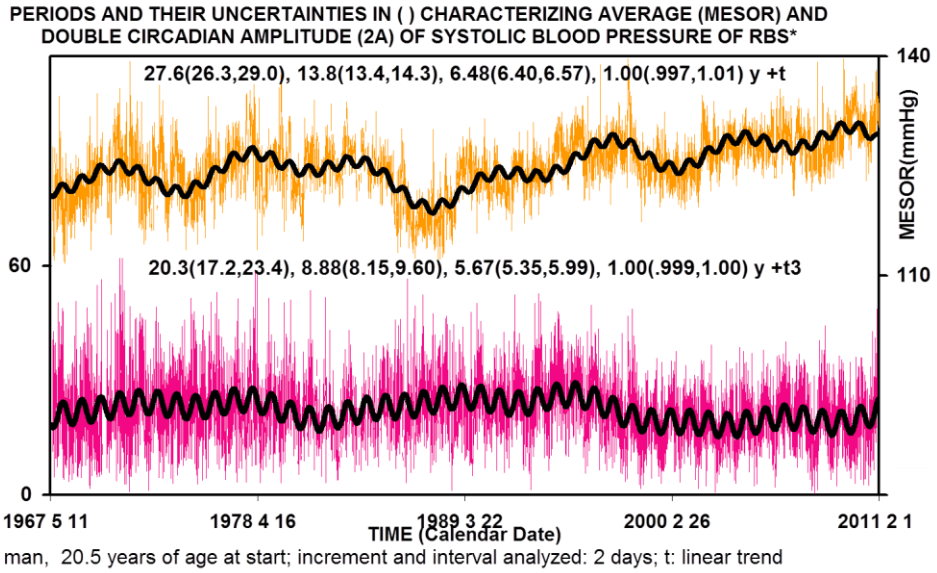


Figure 26A. When analyzed by the extended cosinor, these two new sets of time series of circadian MESORs, Ms, and double amplitudes, 2As, for systolic blood pressure reveal separate sets of periods during the span investigated in the data of a clinically healthy man, RBS. © Halberg.

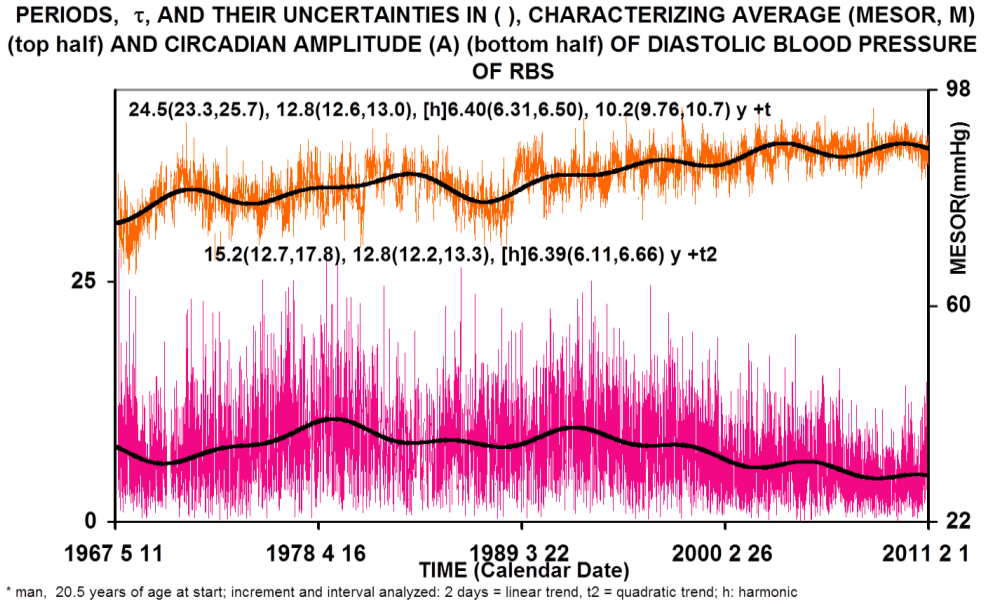


Figure 26B. When analyzed by the extended cosinor, these two sets of time series of Ms and 2As for diastolic blood pressure of RBS reveal separate sets of periods during the span investigated. © Halberg.

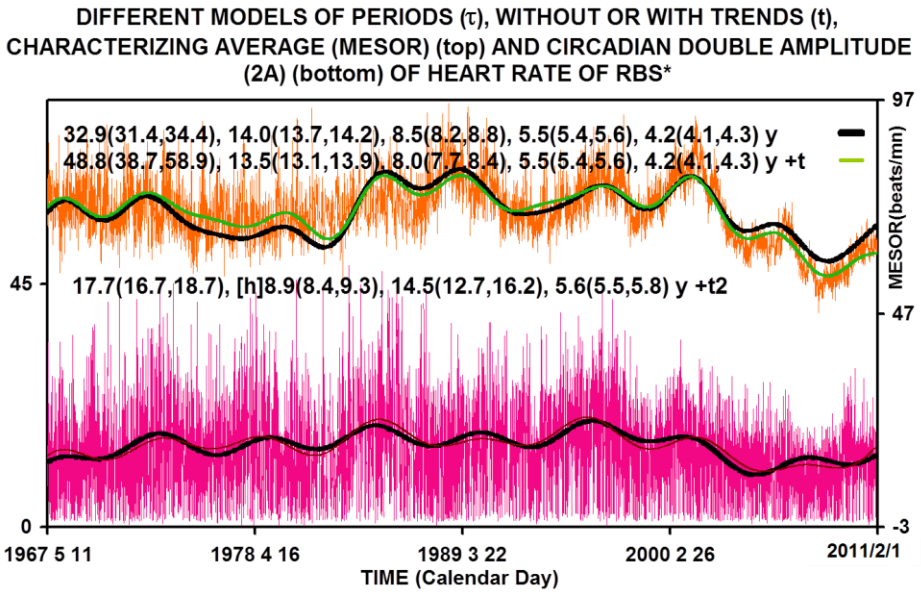


Figure 26C. When analyzed by the extended cosinor, these two sets of time series of Ms and 2As for heart rate of RBS reveal separate sets of periods during the span investigated. © Halberg.

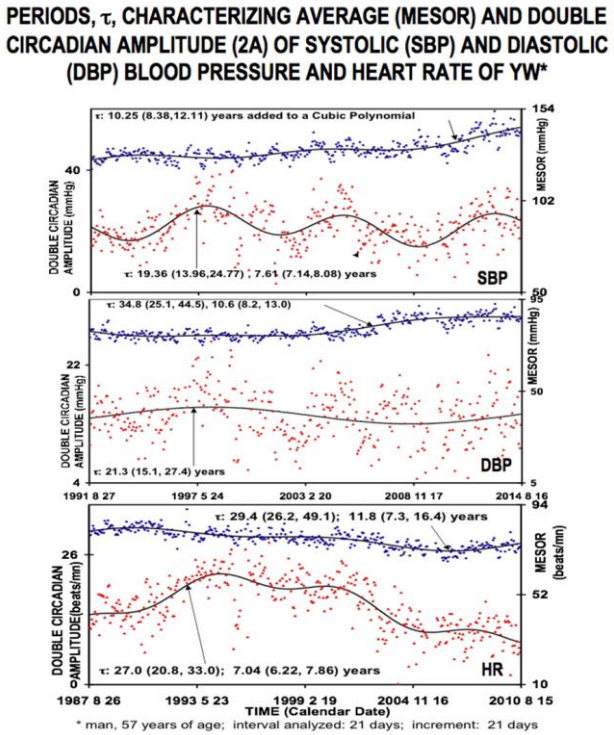


Figure 27. Periods, τ, characterizing average (MESOR) and double circadian amplitude (2A) of systolic (SBP) and diastolic (DBP) blood pressure and heart rate of YW. © Halberg.

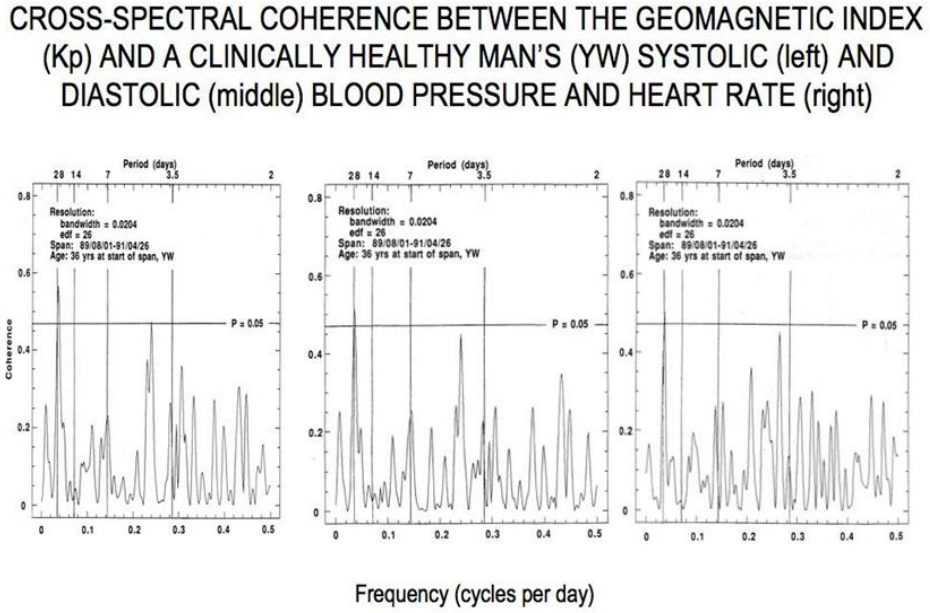
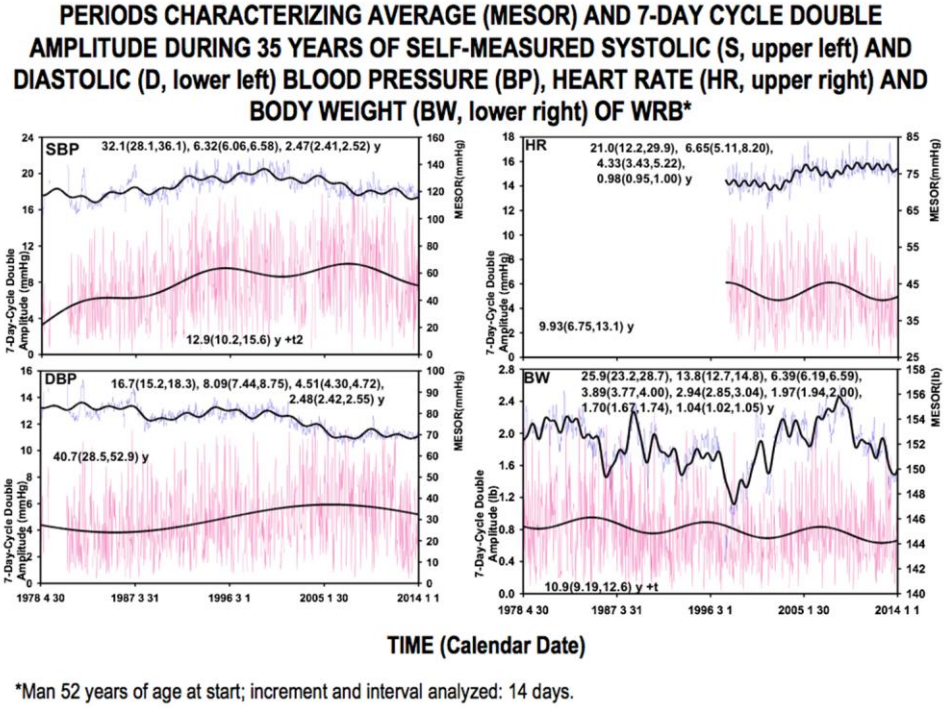


Figure 28. Cross-spectral coherence between the geomagnetic index (Kp) and a clinically healthy man's (YW) systolic (left) and diastolic (middle) blood pressure and heart rate (right). © Halberg.



*Man 52 years of age at start; increment and interval analyzed: 14 days.

Figure 29. Periods characterizing 7-day average (MESOR) and 7-day cycle double amplitude during 35 years of self-measured systolic (S, upper left) and diastolic (D, lower left) blood pressure (BP), heart rate (HR, upper right) and body weight (BW, lower right) of WRB, a man on hypotensive medication. © Halberg.

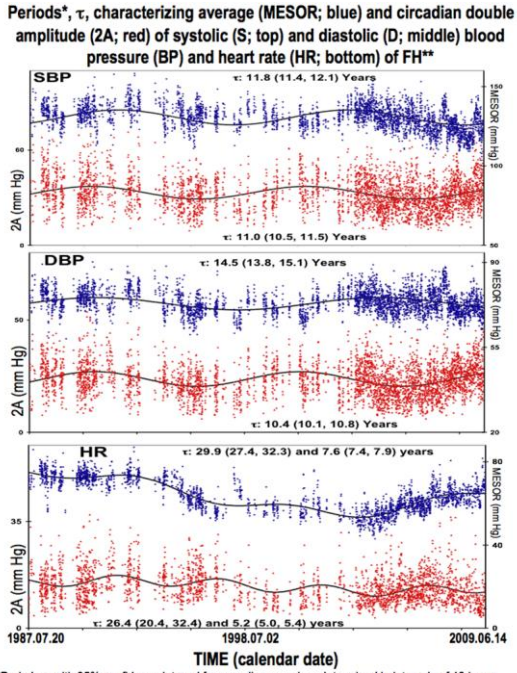


Figure 30. Periods, τ, characterizing average (MESOR, blue) and circadian double amplitude (2A, red) of systolic (S, top) and diastolic (D, middle) blood pressure (BP) and heart rate (bottom) of an elderly man, FH. © Halberg.

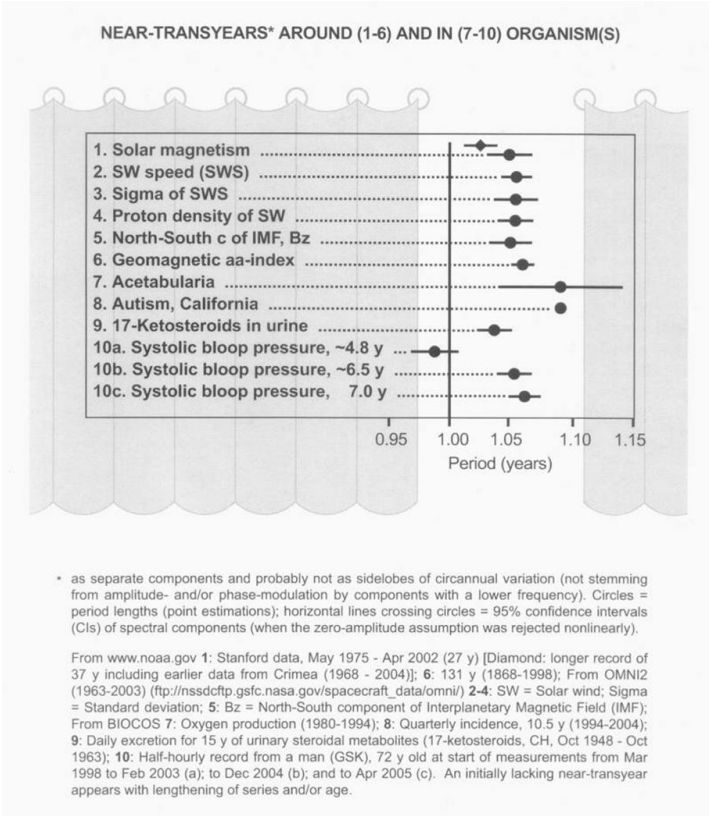


Figure 31A. Near-transyears around (1-6) and in (7-10) organism(s). © Halberg.

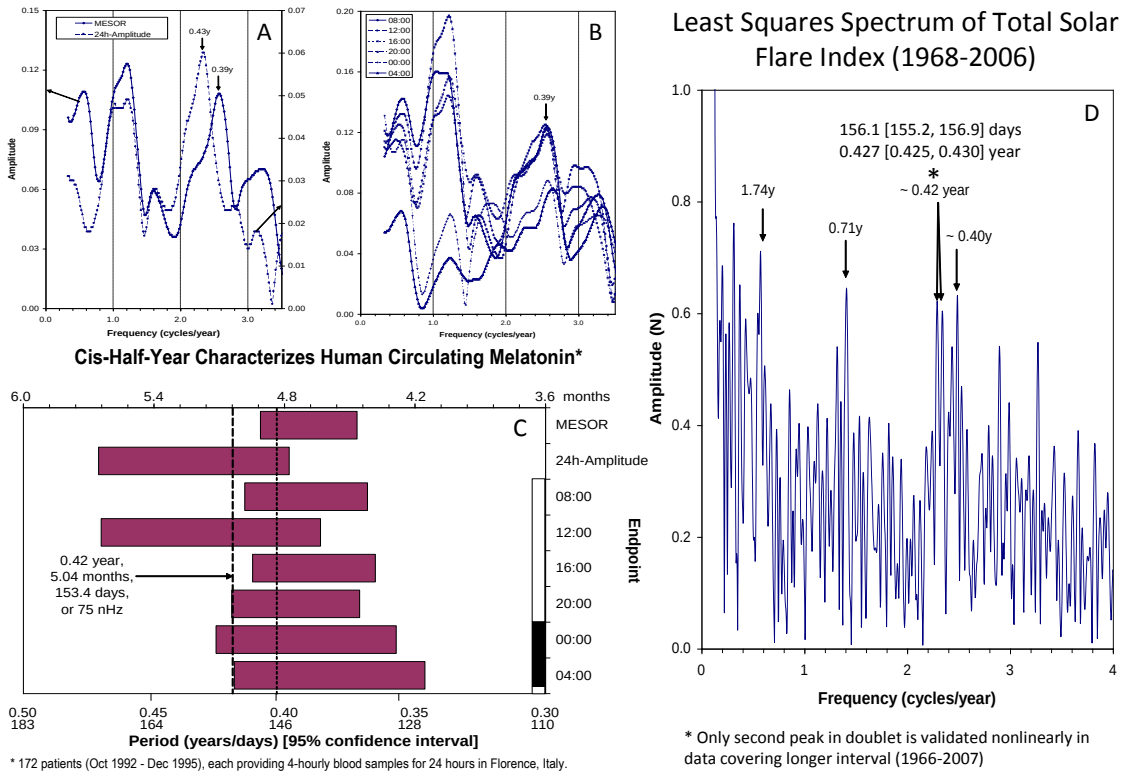


Figure 31B. Section A shows, by a linear estimation, a peak in the circadian amplitude of melatonin at a period, τ, of 0.43 year and a peak in the melatonin MESOR at 0.39 year. These and other analyses in section B are summarized in section C by the extended nonlinear cosinor. The parasemiannual (cis-half-year or quinmensal) peak in section D at ~0.40 year is congruent with analyses of solar flares. Chance can never be ruled out, but it is noteworthy that many among 172 different people (each contributing data only for 24 hours at 4-hour intervals) must be synchronized to show, as a group, a spectral component corresponding in terms of congruence to a component predicted by Wolff and documented by Rieger et al., and many others (*Table 3*). © Halberg.

GLOCAL (top, middle) ANALYSIS OF SOLAR FLARES (SFI) AND LOCAL (bottom) ANALYSIS OF HEART RATI

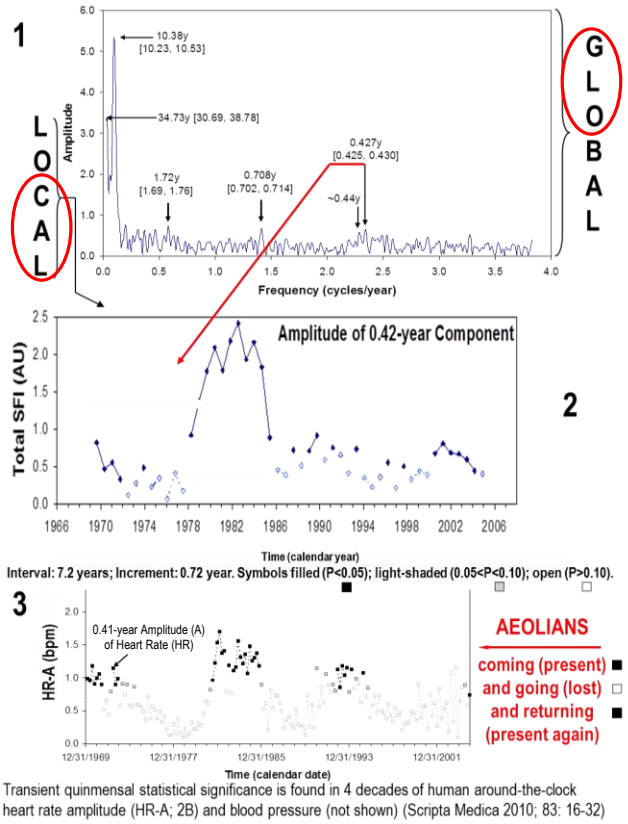


Figure 31C. Spectral window of solar flares from 1966 to 2007 (top left, 1) shows, with a prominent ~10.38-year Horrebow-Schwabe and a lesser ~34.73-year Brückner-Egeson-Lockyer (BEL) peak (see Figure 3), an ~0.43-year quinmensal cycle (top 2 rows) with coexisting ~0.71- and ~1.72-year components. The statistical significance of these components, as shown for the quinmensals in flares (row 2) and in human heart rate (bottom row), and elsewhere for the BEL (16), waxes and wanes, as shown by filled (P<0.05) and empty (P>0.05) symbols for the rejection of the zero-amplitude assumption. © Halberg.

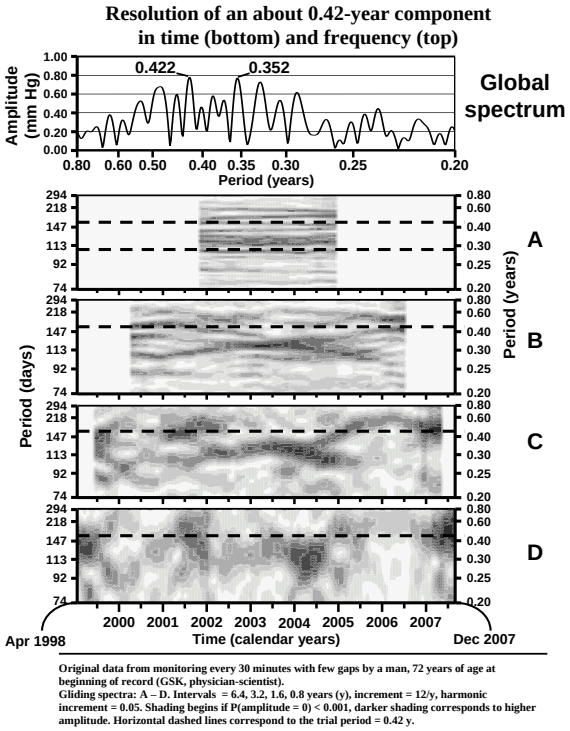


Figure 31D. Global (spectral window of the entire series; top row) and local (gliding spectral windows with intervals of different lengths; rows below) analyses of diastolic blood pressure of an elderly man, GSK, show aeolian quinmensals. © Halberg.

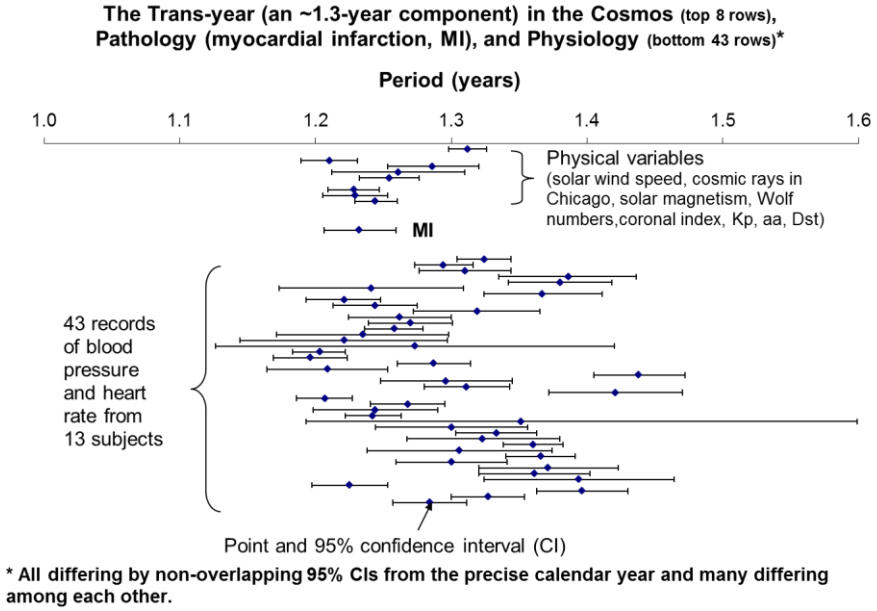


Figure 32. The transyear (an ~1.3-year component) in the cosmos (top 8 rows), pathology (myocardial infarction, MI) and physiology (bottom 43 rows), all differing by non-overlapping 95% CIs from the precise calendar year and some differing among each other. © Halberg.

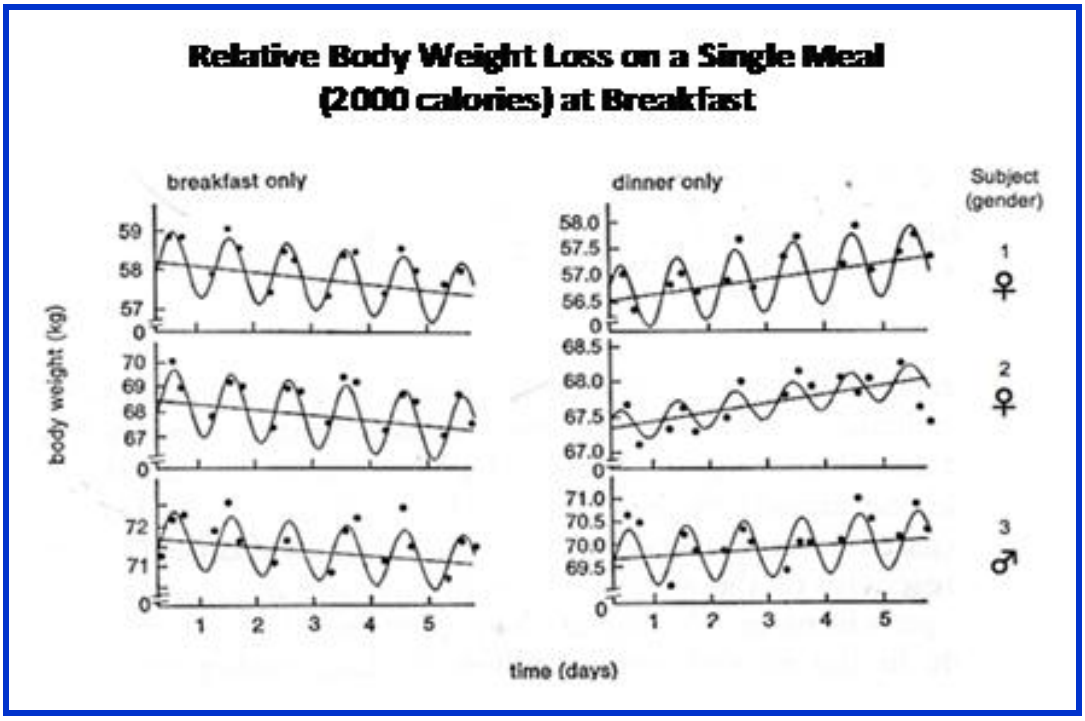


Figure 33A. Body weight loss on breakfast-only vs. body weight gain on dinner-only in 3 young clinically healthy subjects consuming a single daily meal of 2000 calories. In this limited study, a 24-hour cosine function and a linear trend fitted concomitantly to the data were statistically significant 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, Figures 33B-33G. © Halberg.

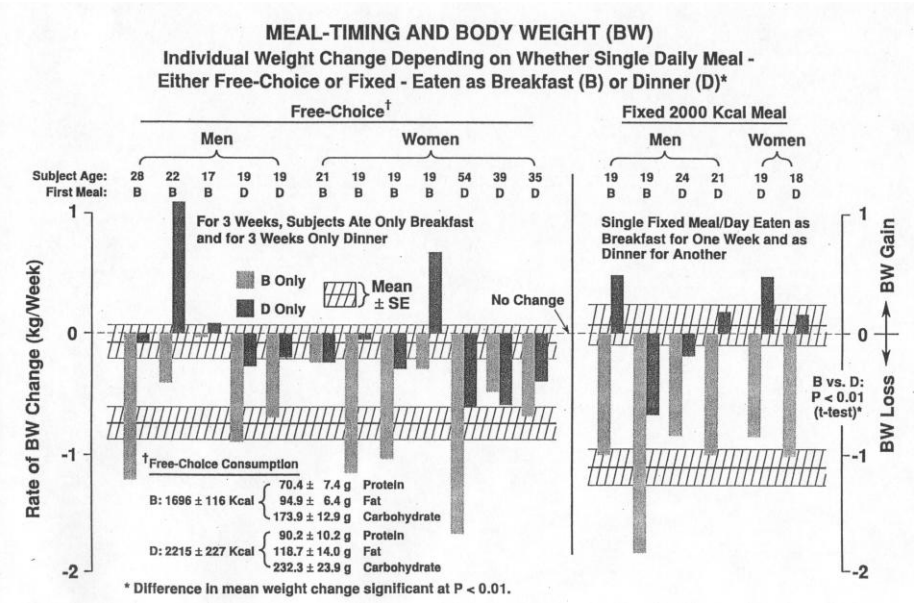


Figure 33B. Meal timing and body weight. In two separate studies of the effect of meal timing on body weight, 9 men and 9 women consumed either a fixed 2,000-calorie meal or a single

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/wk was noted on breakfast-only. The rate of body weight change also differed significantly ($P<0.02$) between the two schedules. © Halberg.

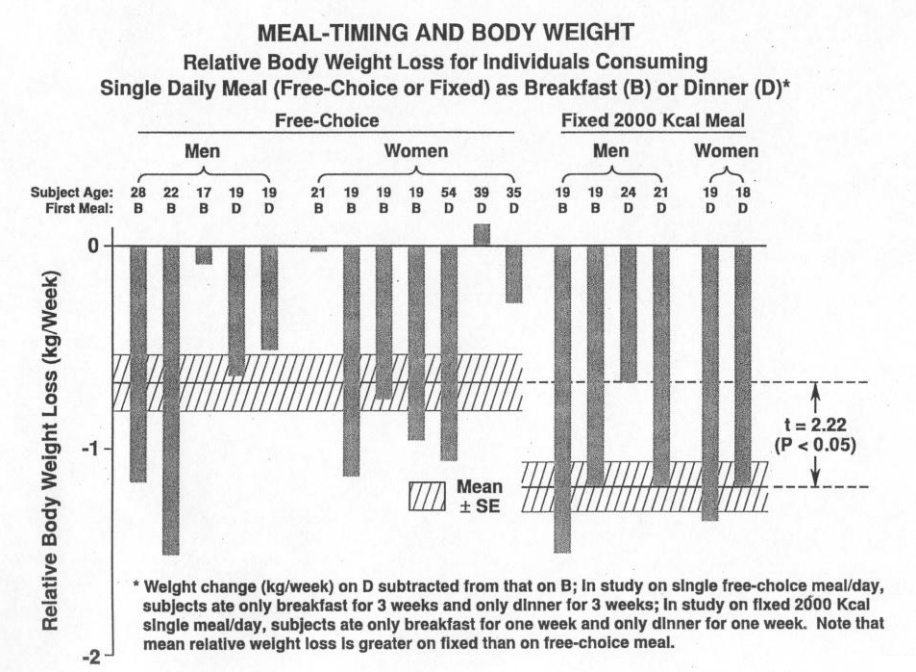


Figure 33C. Relative body weight loss on breakfast only vs. dinner only for each subject participating in the two studies described in Figure 33B. Only one volunteer gained weight on breakfast vs. dinner. Overall, the difference in relative body weight loss on breakfast (B) vs. dinner (D) is statistically significant ($P<0.05$), whether a fixed 2,000-calorie meal (right) or a single free-choice meal (left) is consumed. Weight change (kg/wk) 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.

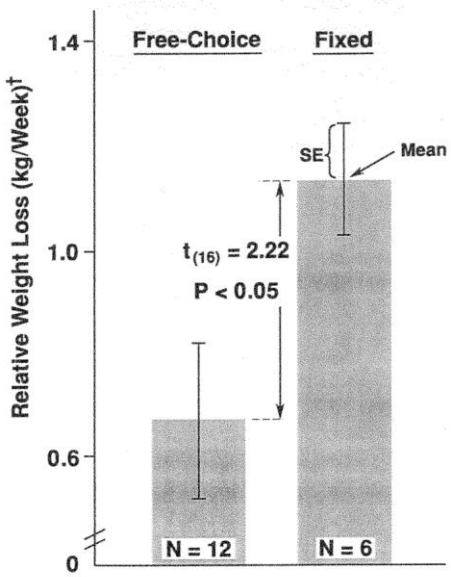
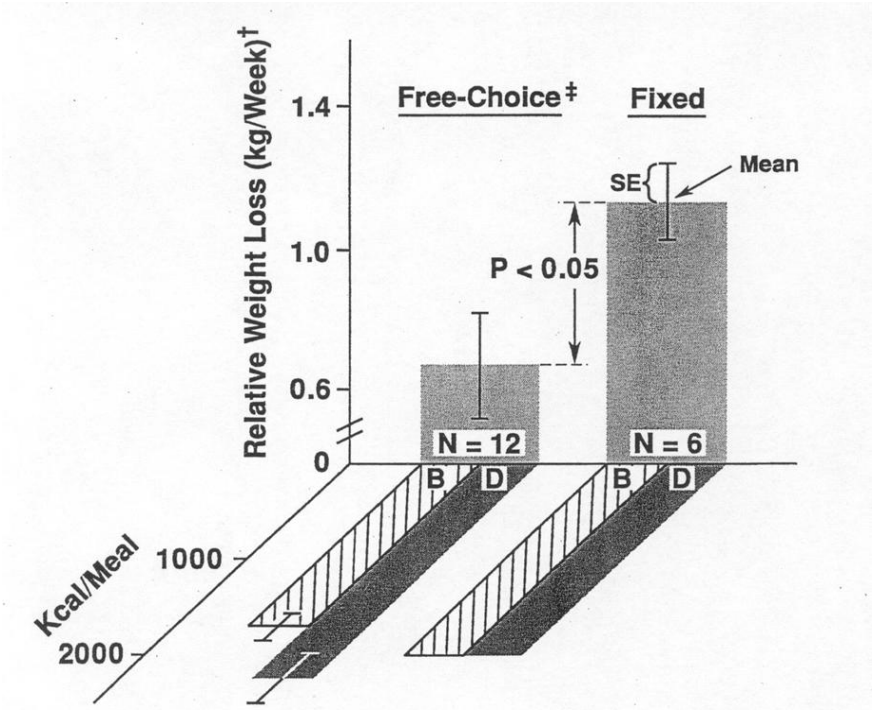


Figure 33D. Appetite (here defined as choice and amount of food) modifies the effect of meal timing on body weight. Relative body weight loss on breakfast-only (B) as compared to dinner-only (D) is less when meal is free-choice rather than fixed. An overall summary of relative body weight loss on breakfast-only 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.



* Here defined as choice of kind and amount of food.

† Weight change (kg/week) on B subtracted from that on D.

‡ Average free-choice intake (± SE) on B = 1696 ± 116 Kcal/meal, on D = 2215 ± 227 Kcal/meal; former value significantly different from 2000 (t = 2.62; P < 0.05), latter not. Food consumed consisted on the average of

g		Protein	Fat	Carbohydrate
Free-Choice	B	70.4 ± 7.4	94.9 ± 6.4	173.9 ± 12.9
	D	90.2 ± 10.2	118.7 ± 14.0	232.3 ± 23.9
Fixed Meal, B & D		77.0	75.0	250.0

Figure 33E. 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.

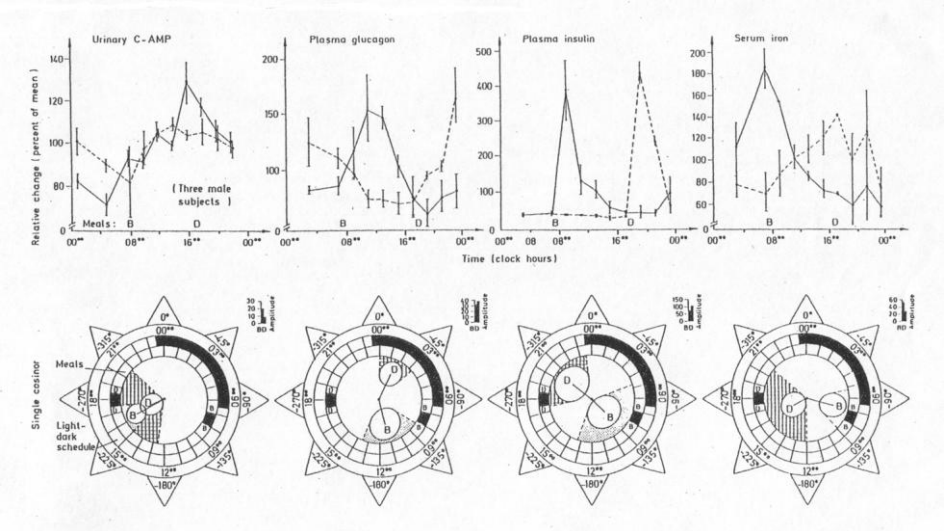


Figure 33F. Consuming a single daily meal as breakfast-only vs. dinner-only affects the timing of the circadian chronome component differently for different physiological variables in humans. The single daily meal was 2,000 calories given for 7-day spans. Breakfast (B), solid line. Dinner (D), broken line. © Halberg.

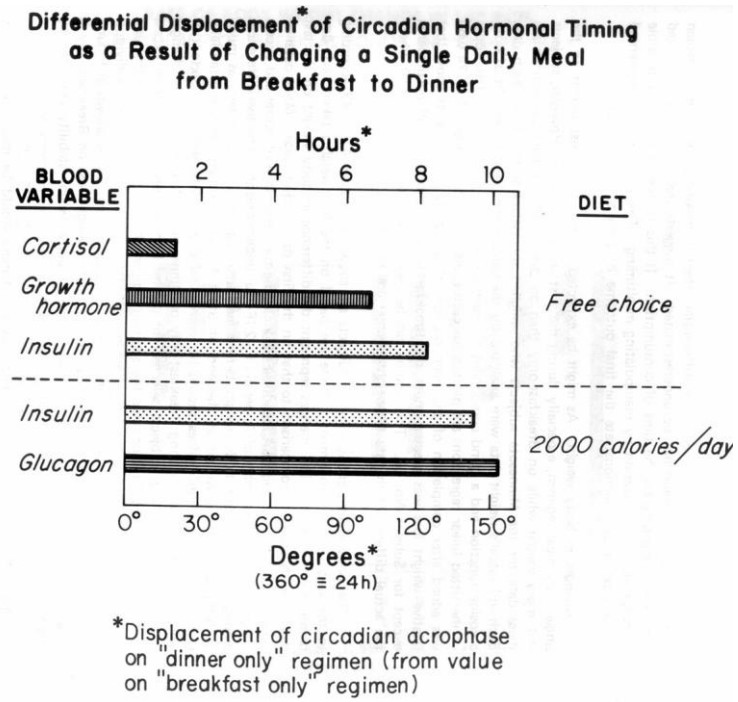


Figure 33G. Differential displacement of circadian hormonal timing as a result of changing a single daily meal from breakfast to dinner. Whereas the circadian rhythm of circulating cortisol is only slightly affected by the timing of a single daily meal, considerable phase-shifts are observed for the case of growth hormone, insulin, and glucagon, resulting in a different internal timing of the latter three hormones vs. cortisol. © Halberg.

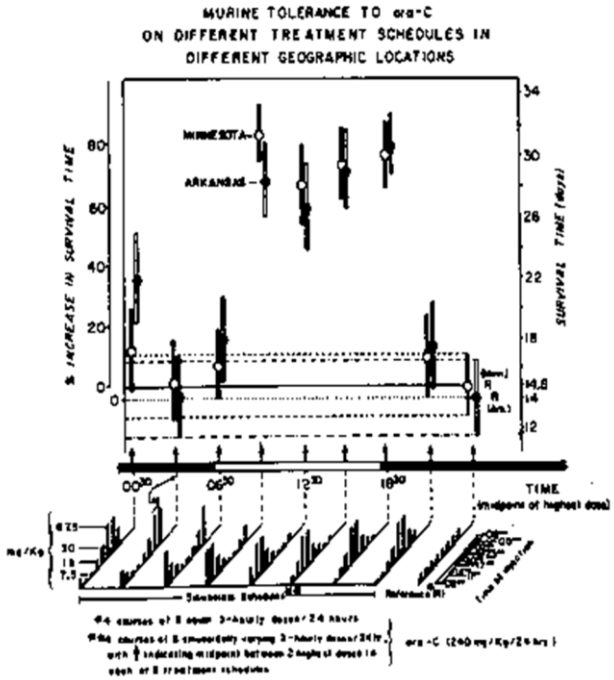
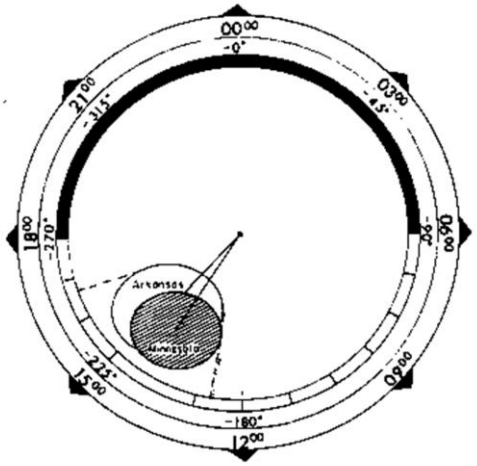


Figure 34A. Chronotoxicology: comparison of equal dose (homeostatic) ara-C treatment of L1210 leukemia (extreme right) with sinusoidal doses in Arkansas and Minnesota reveals similar gain in survival from certain timings of sinusoidal variation of the same total dose (78). © Halberg.



	Mesor (M)* M ± SE	Amplitude (A)* A ± SE	Acrophase (Φ)** Φ	95%CI	% Rhythm	P-value F-test
Minnesota	554 ± 22	206 ± 31	-21°	-188°, -233°	22	.01
Arkansas	560 ± 24	167 ± 34	-221°	-191°, -251°	13	.01

N = 180 mice (20/time point) in each location

*In hours

**From local midnight

Figure 34B. Agreement of ara-C chronotherapy timing in Arkansas and Minnesota revealed by cosinor with overlapping uncertainties. © Halberg.

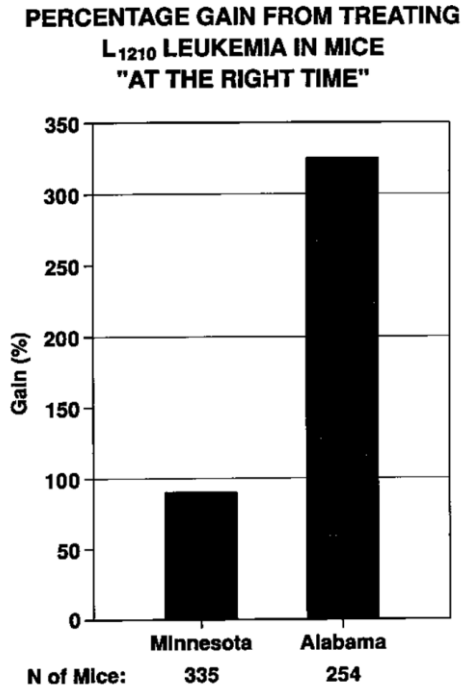


Figure 34C. Investigators in Alabama (Rose et al., Cancer Treatment Rep 1978; 62: 1337-1349) did not find a difference (in survival times only of those mice that died) between their homeostatic treatment and chronotherapy (cured mice were ignored). Accounting for cures in turn shows a clear benefit from a sinusoidal treatment, actually a much bigger gain in Alabama than in Arkansas and Minnesota. © Halberg.

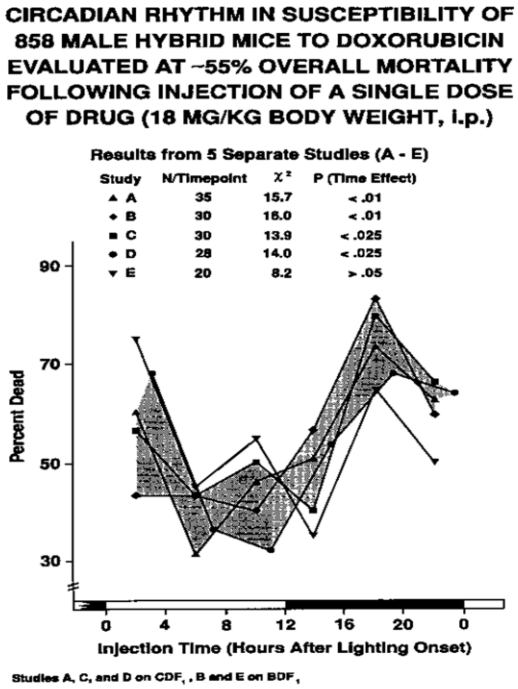


Figure 34D. Circadian variation in toxicity of doxorubicin. © Halberg.

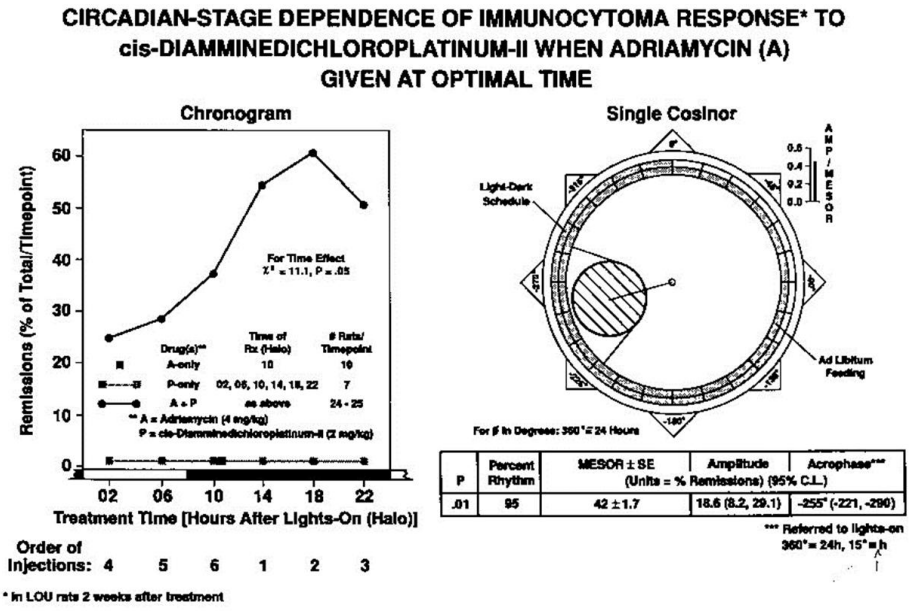


Figure 34E. Circadian variation in effectiveness of doxorubicin (adriamycin). © Halberg.

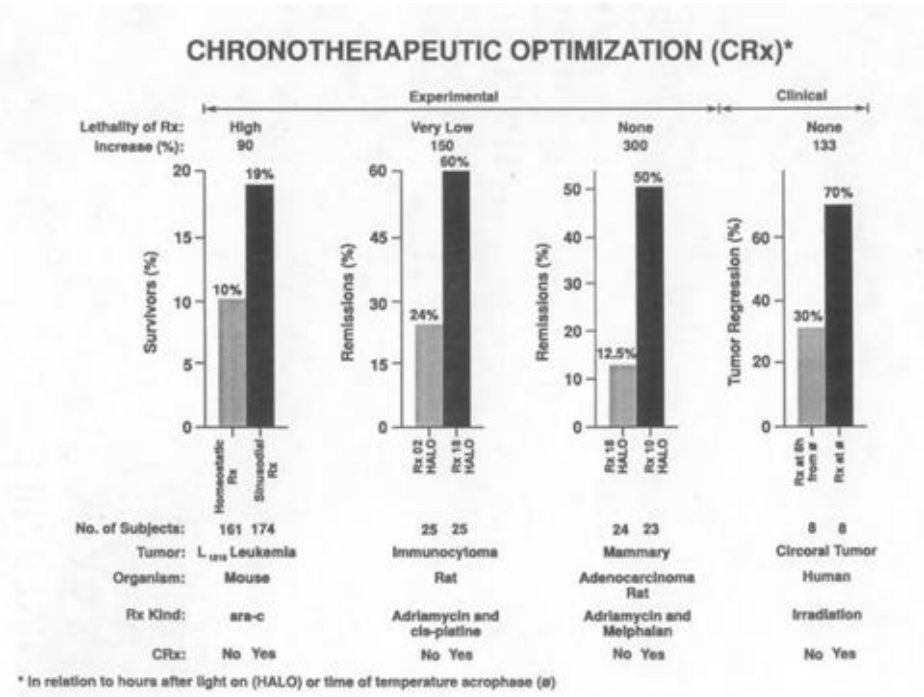


Figure 34F. Gains from cancer chronotherapy: experimental and clinical. © Halberg.

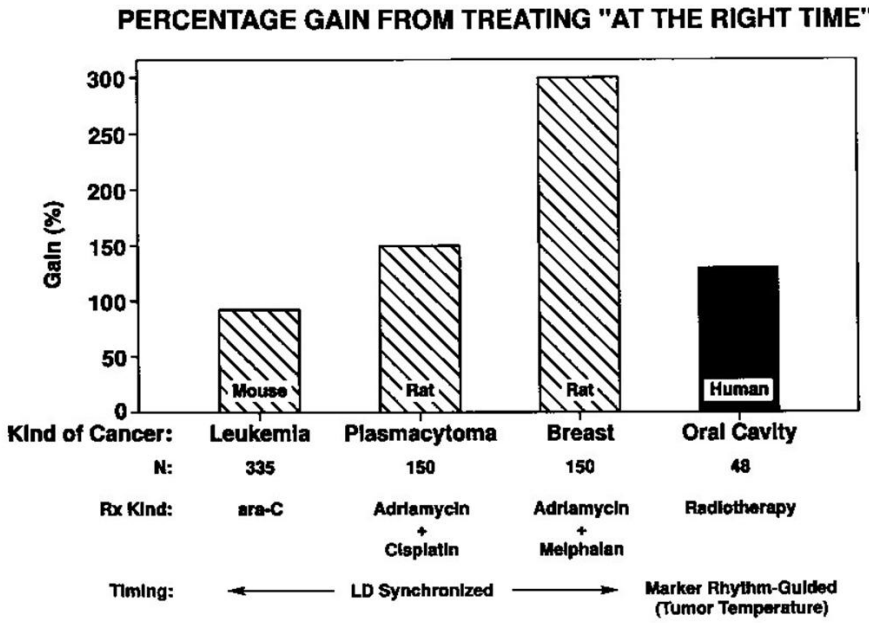


Figure 34G. Gains from cancer chronotherapy: experimental and clinical. © Halberg.

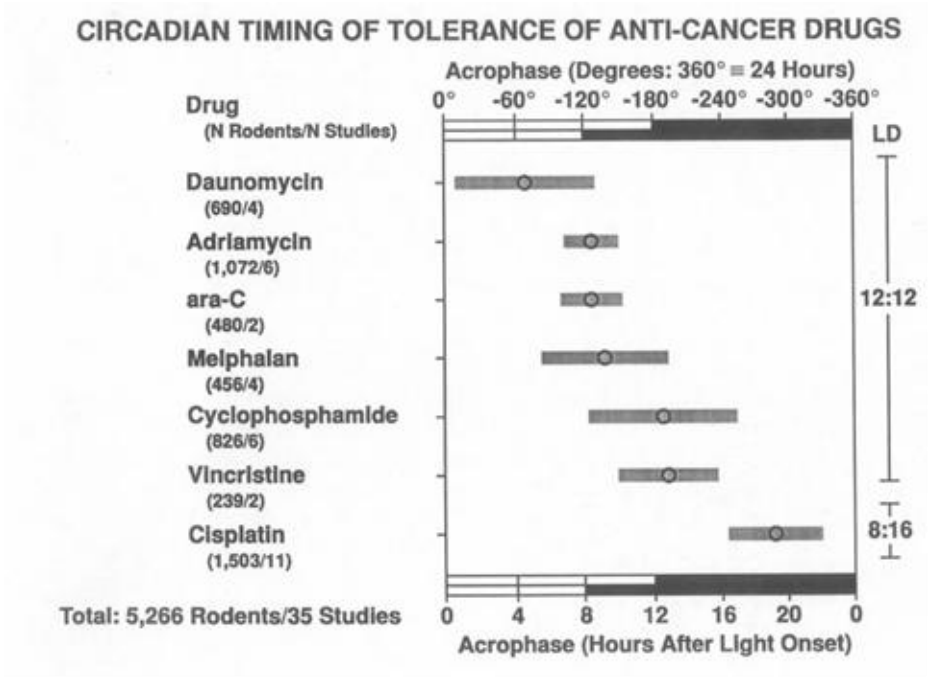


Figure 34H. Timing cancer chronotherapy depends on the drug used. © Halberg.

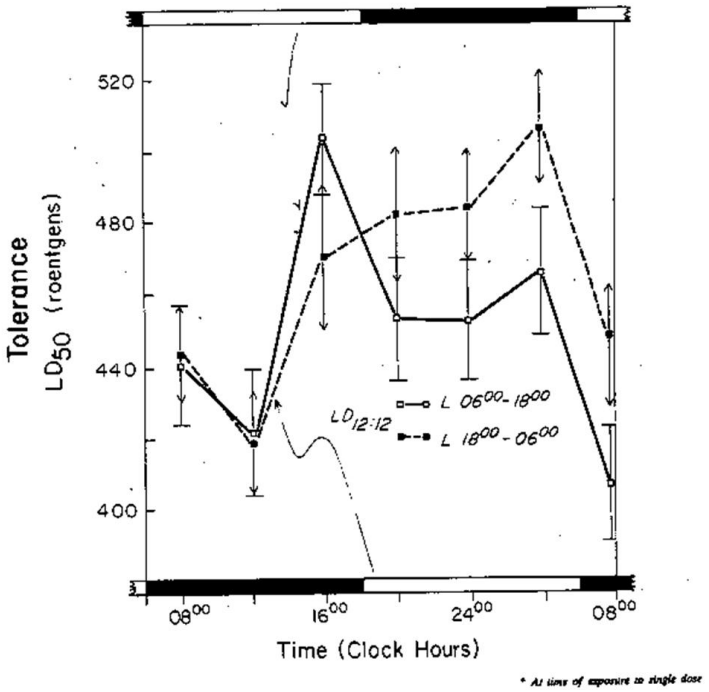


Figure 34I. Chronotolerance of whole body irradiation. © Halberg.

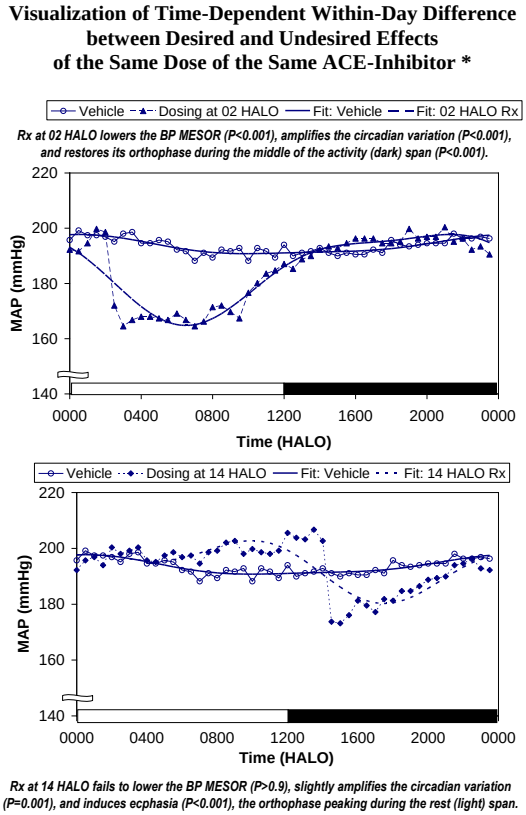
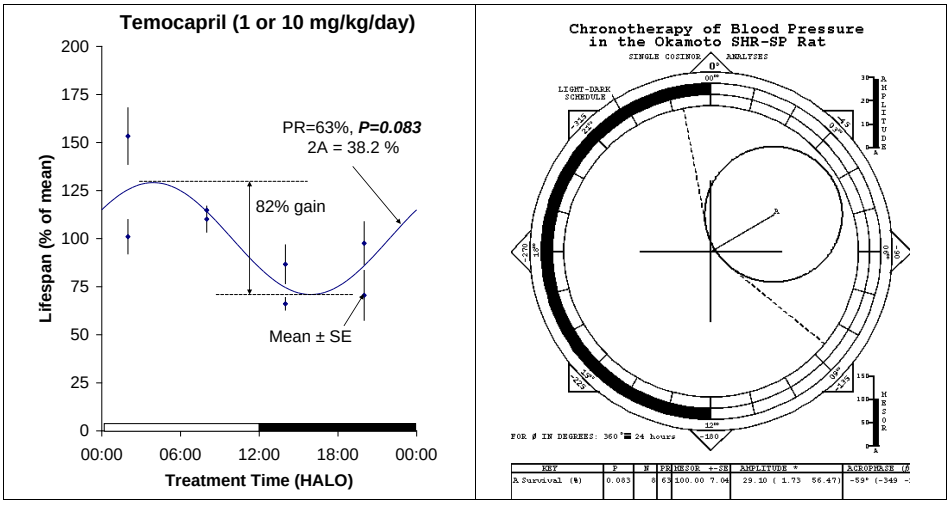


Figure 34J. Circadian stage-dependence of antihypertensive response in SHR-SP rats. Original data of Akio Fujimura (128). © Halberg.

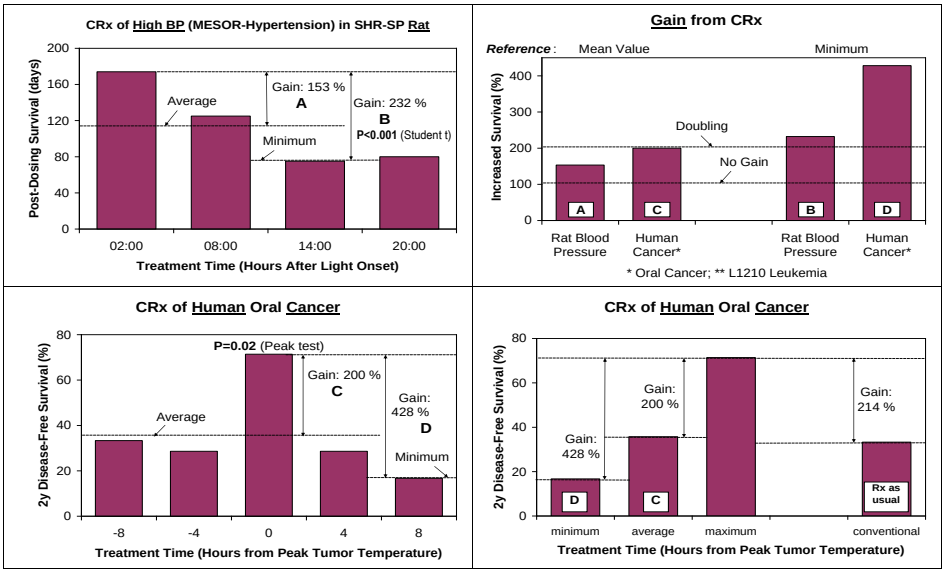
Survival of Salt-Loaded Okamoto SHR-SP Rats Treated at Different Circadian Stages #



with an angiotensin converting enzyme inhibitor. Circadian rhythm demonstrable with borderline statistical significance after pooling data at two doses (after expressing data as a percentage of respective overall mean values). Note that best treatment time may occur at time other than actual test times (slightly later than 02 HALO in this case), albeit 95% confidence limits of acrophase include

Figure 34K. Summary of circadian stage-dependence of antihypertensive response in SHR-SP rats. Original data of Akio Fujimura (128). © Halberg.

Better than Doubling Survival Achieved by Chronotherapy (CRx) *



* In the case of blood pressure with 1mg/kg/day Temocapril in salt-loaded stroke-prone Okamoto (SHR-SP) rats (top left) and by radiation of human cancers of the oral cavity timed by marker rhythmometry (of tumor temperature) (bottom left); Therapeutic gain assessed by comparing response at best time with average response or response at worst time (top right), or in the case of chronoradiotherapy, also with response to conventional treatment administered with timing during "regular hours" by convenience

Figure 34L. Chronotherapeutic gain in laboratory and clinic. © Halberg.

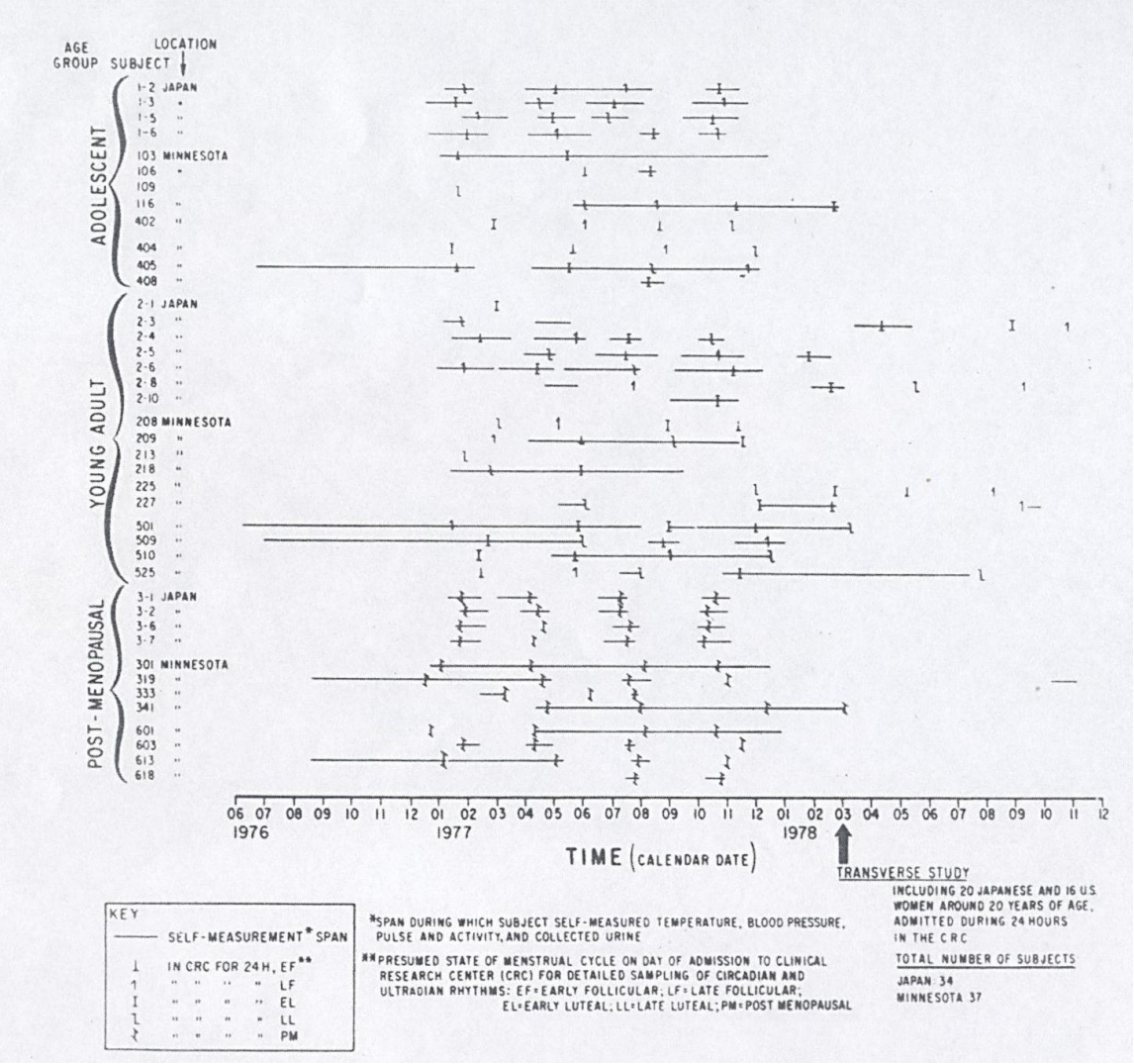


Figure 35A. Individual sampling schemes (spans) for assessment of multifrequency rhythms in human blood and urine. Experimental design of Minnesota-Japan chronoepidemiologic study on women of 3 age groups: schedule of hospital admission and at-home self-measurements of subjects classified according to age and geographic location, with specification of menstrual cycle stage on day of admission. Limitation: ignorance, at the time, of quinmensals and transyears discovered later in some other hormones that remain to be examined. © Halberg.

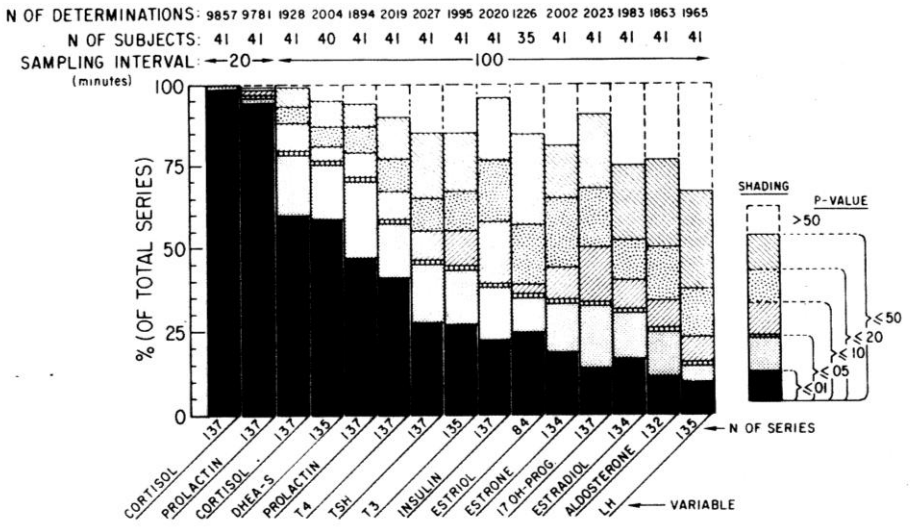


Figure 35B. Comparison of statistical significance of circadian rhythm, assessed by least-squares fit of a 24-hour cosine curve for 13 hormones in plasma of healthy women sampled for individualized rhythm assessment by cosinor. P from F-test of zero-amplitude hypothesis. Since the hierarchical statistical significance represented by P-values is sampling-dependent, prolactin and cortisol, measured every 20 min, were also analyzed at 100-min intervals as for the other hormones. Total number of determinations: 40,765. © Halberg.

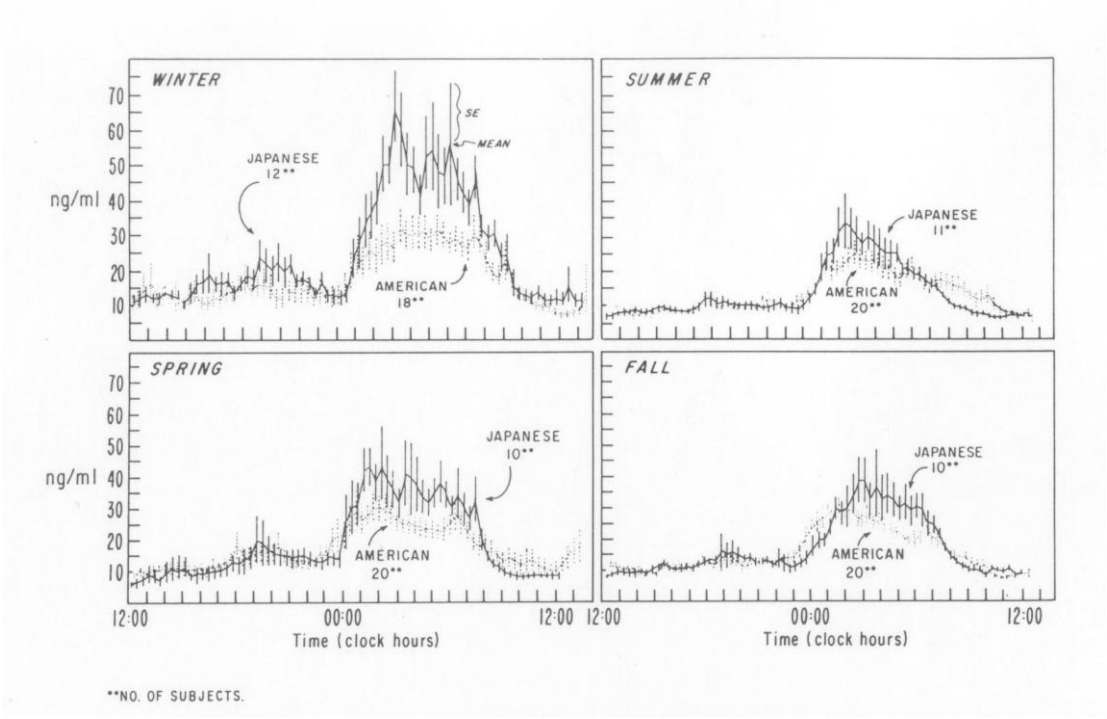


Figure 35C. Comparison of plasma prolactin in clinically healthy Japanese and Minnesotan women in four seasons. Samples taken at 20-min intervals over a 24-hour span in Fukuoka City, Japan, and Minneapolis, Minnesota, USA. © Halberg.

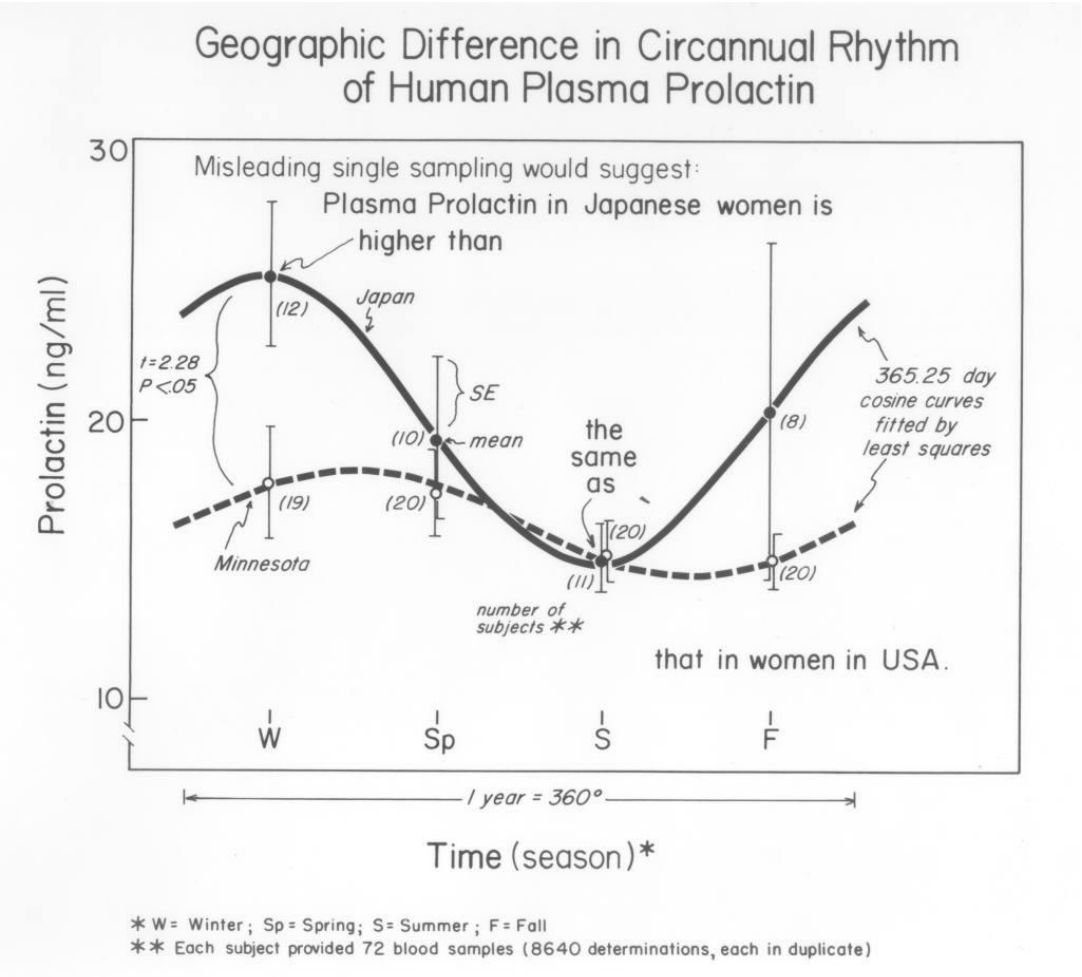


Figure 35D. Geographic difference in circannual rhythm of human plasma prolactin. Contradictory comparisons of circadian MESOR could be obtained by sampling in different seasons. Moreover, controlling only time of year (or only time of day) may not avoid misleading results due to circannual (or circadian, as the case may be) variations, whereas assessment of circannual (or circadian) rhythm characteristics may reveal important chronoepidemiological or chronoprotopathological results (as would most likely extended focus on rhythms discovered in the interim). Conclusions from single samples obtained in different seasons (or times of day) can be resolved as differences of circannual (circadian) prolactin rhythm between Japanese and American women. Each subject provided 72 blood samples (8,640 determinations, each in duplicate). W, winter; Sp, spring; S, summer; F, fall. © Halberg.

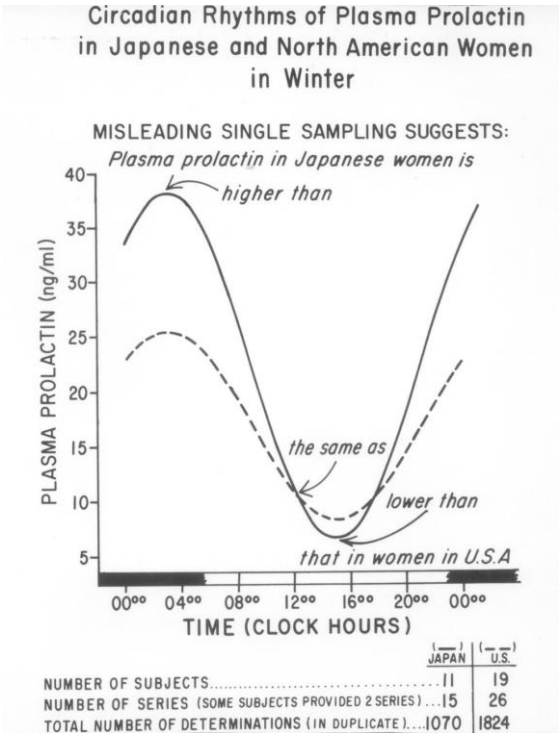


Figure 35E. Circadian rhythm of plasma prolactin in Japanese and North American women in winter. Dense sampling on plasma prolactin suggests both a larger circadian amplitude and a higher rhythm-adjusted mean or MESOR in Japanese as compared to North American women ($P<0.002$ from Hotelling T^2 test). © Halberg.

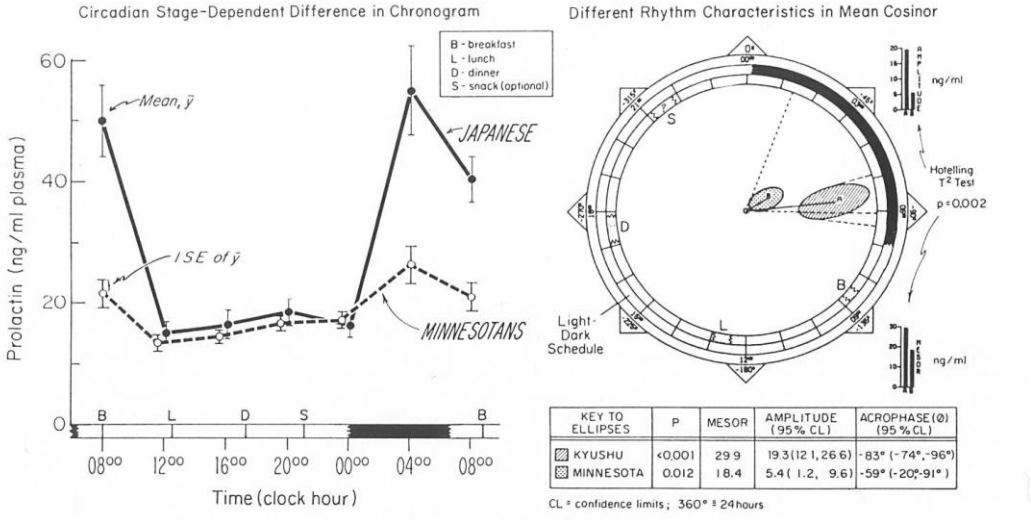


Figure 35F. Difference of plasma prolactin between clinically healthy Japanese and American women in March 1978 when circannual rhythm is near its maximum, confirmed by complementary study. Fifteen whites of mixed ethnic background (18-24 years old) in Minnesota and 20 Japanese (~20 years old) in Kyushu, Japan. © Halberg.

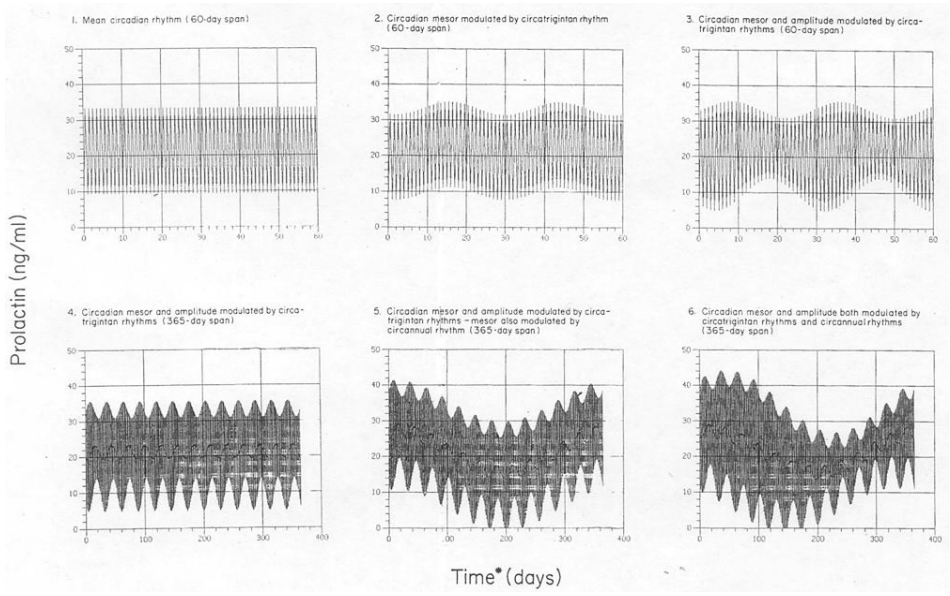


Figure 36. Stepwise theoretical reconstruction of partial spectral structure of human plasma prolactin for group of Japanese women (based on parameter estimates obtained from separate least-squares fits of cosine curves with periods of 24 hours [circadian], 28 days [circatrigintan] and 365 days [circannual] to data on plasma prolactin obtained every 20 min for 24 hours, ~4 times a year on a few women). Didactic example modeling the interaction of human plasma prolactin rhythms with different frequencies, including modulation of circadian MESOR and amplitude by circatrigintan and circannual rhythms. © Halberg.

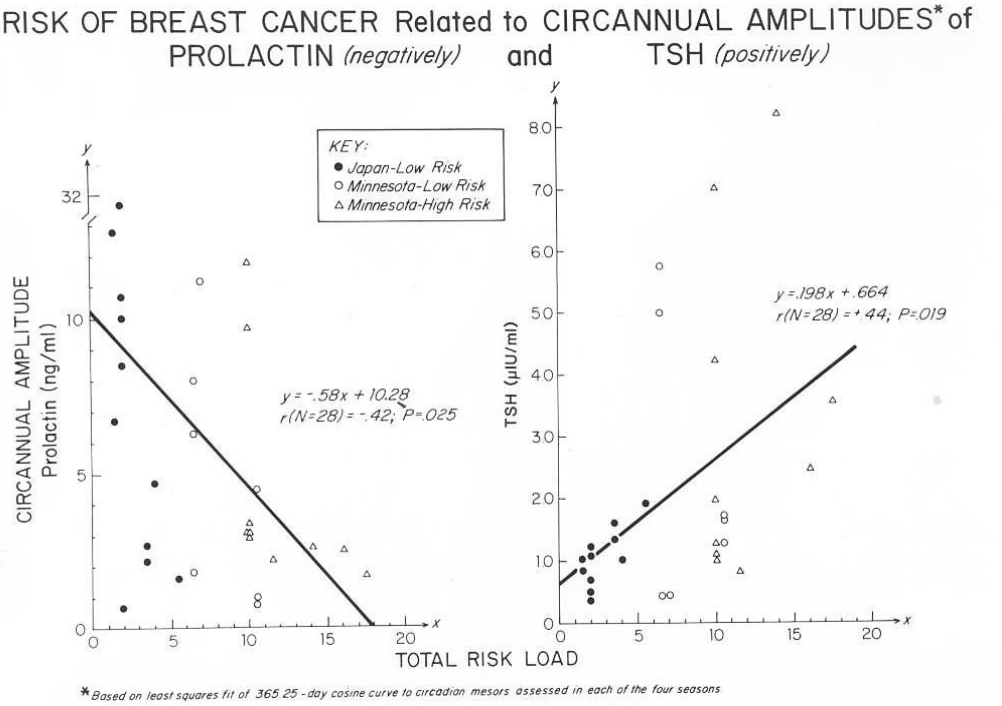


Figure 37. A negative correlation between the total relative breast cancer risk evaluated from

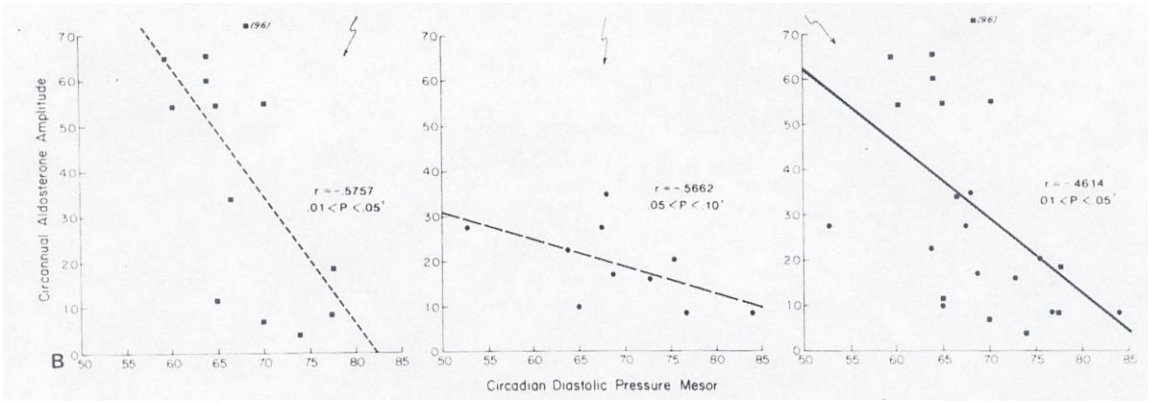
epidemiological criteria and the circannual prolactin amplitude (left) corroborates the finding that an evaluation of breast cancer risk is associated with a decrease in circannual amplitude (based on least squares fit of 365.25-day cosine curve to circadian MESORs assessed in each of the four seasons). Note further the positive correlation between epidemiologically assessed breast cancer risk and the circannual amplitude of thyroid-stimulating hormone (TSH) (right). Clinical thyroid malfunction has empirically been associated with breast cancer risk. If, then, this topic is still controversial, this may perhaps be accounted for by the circannual stage-dependence of the correlation.

It is also noteworthy that in prostatic cancer (a condition characterized by geographic differences in morbidity and mortality similar to those of breast cancer), the extent of circannual variation also changes as a function of risk and/or cancer. In blood sampled with serial independence in the morning at different times of the year, a prominent circannual rhythm in TSH of healthy subjects is lost in prostatic cancer (and perhaps even in men at high risk of prostatic cancer). For prolactin, a circannual rhythm becomes demonstrable in the case of prostatic cancer, while it is not demonstrable with serially independent sampling in healthy men of low or high prostatic cancer risk.

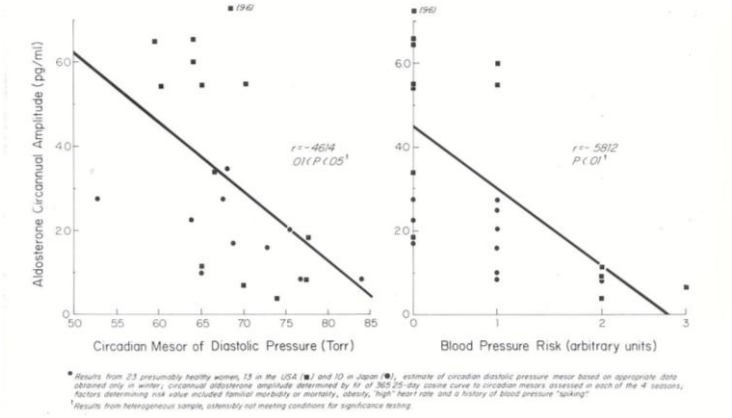
Thus, TSH and prolactin show opposite behavior along the 1-year scale in cancers of both breast and prostate (rather than responding in the same way, as is the case along the scale of minutes to hours, following the application of stimuli such as thyrotropin-releasing hormone).

The two correlations shown in the figure are just part of a larger correlation matrix. The circumstance is noted that correlations emerged as statistically significant for the very hormones which clinicians have long considered have some relation to breast cancer, yet thus far could not rigorously establish such a relation as biologically significant, perhaps because of too-limited sampling.

While these conclusions rest on large samples, they describe only a small number of subjects. Moreover, all conditions required to apply a linear regression between two variables are not satisfied. A test for lack of fit indicates that the model is not adequate for TSH; the error term is not normally distributed. In addition, the assumption of homogeneity of variance is not verified for prolactin as well as for TSH. Finally, in the case of prolaction, there seems to be an age effect on both this circannual amplitude (decreases with age) and the breast cancer risk (increases with age). This may account for the negative correlation illustrated in the figure. Hence the correlations in the figure are of ordering rather than documenting value. They are intended to emphasize that circannual rhythmicity deserves further study in relation to carcinogenesis. If such correlations can be confirmed and if the circannual rhythms involved should prove to be determinants of carcinogenesis in the human breast, these same correlations will point to the possibility of a chemoprevention of breast cancer.



Circadian Mesor of Diastolic Blood Pressure (left) and Risk of Diseases Associated with High Blood Pressure (right) Inversely Related to Circannual Amplitude of Plasma Aldosterone*



*Results from 23 presumably healthy women, 13 in the USA (■) and 10 in Japan (●), estimate of circadian diastolic pressure mesor based on appropriate data obtained only in winter; circannual aldosterone amplitude determined by fit of 365.25-day cosine curve to circadian mesors assessed in each of the 4 seasons; factors determining risk value included familial morbidity or mortality, obesity, "high" heart rate and a history of blood pressure "spiking".
†Results from heterogeneous sample, ostensibly not meeting conditions for significance testing.

Figure 38. Top: Negative correlation between the circannual aldosterone amplitude (based on least squares fit of 365.25-day cosine curve to circadian MESORs assessed in each of the four seasons on each of the women investigated in Minnesota and Japan) and the circadian diastolic blood pressure MESOR (in winter, the season when blood pressure profiles at about 10-minute intervals were obtained in both locations) observed in women in Minnesota (N=13, left), in Kyushu, Japan (N=10, middle) and both (N=23, right). Bottom: Negative correlation of the circannual aldosterone amplitude and both the circadian diastolic blood pressure MESOR and the individual risk of diseases associated with high blood pressure. Results from 23 presumably healthy women, 13 in the USA (■) and 10 in Japan (●); estimate of circadian diastolic blood pressure MESOR based on appropriate data obtained only in winter; circannual aldosterone amplitude determined by fit of 365.25-day cosine curve to circadian MESORs assessed in each of the four seasons; factors determining risk value included familial morbidity or mortality, obesity, "high" heart rate and a history of blood pressure spiking. The same restrictions as outlined for Figure 35G applies to Figure 36 and this figure. For qualification, see legend of Figure 37 © Halberg.

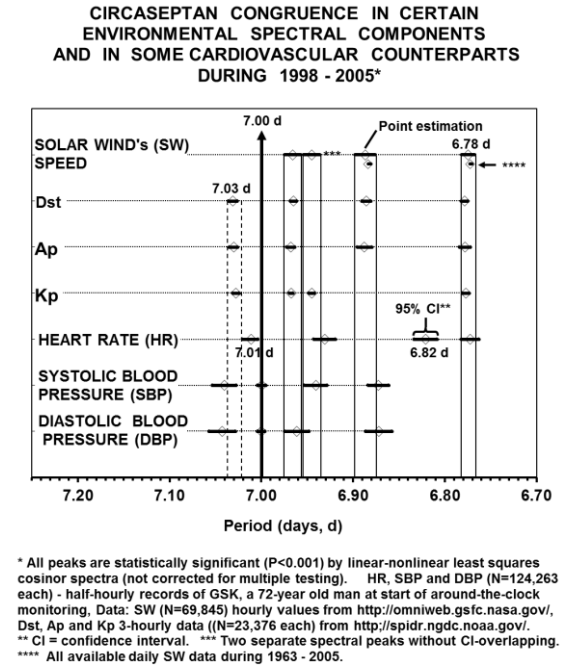


Figure 39A. Transdisciplinary congruence, defined by overlapping 95% confidence intervals of the periods in the circaseptan spectral region. © Halberg.

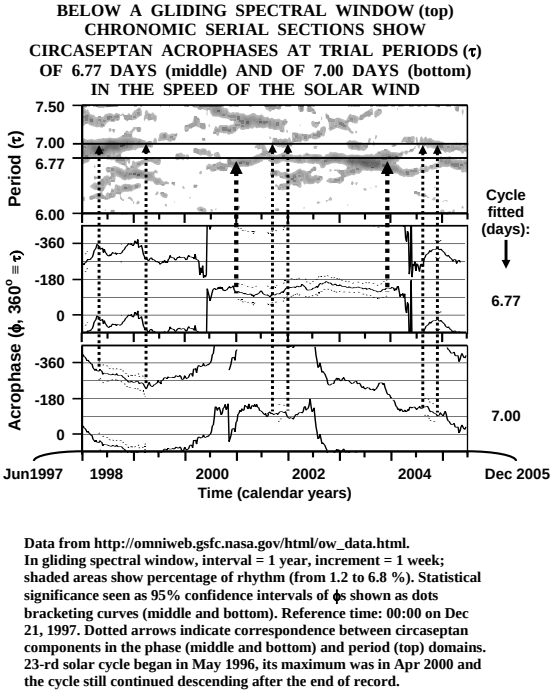


Figure 39B. Combination of gliding spectral window (top) with special focus on the behavior of two selected periods (serial sections, middle and bottom), with the time course of the phase validating the 6.77-period by a more or less horizontal trajectory of phases in only part of the record, but invalidating a precise 7-day periodicity since no dots bracket any horizontal time course of phases, and the small initial section with dots shows a gradual advance. © Halberg.

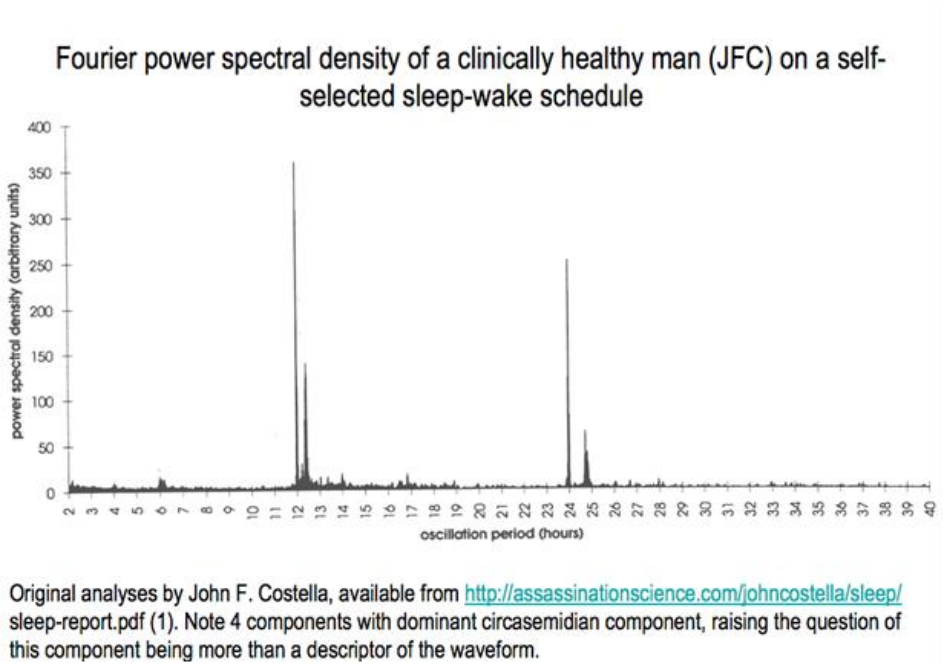


Figure 39C. Fourier power spectral density of rest-activity of a clinically healthy man (JFC) on a self-selected sleep-wake schedule (66). © Halberg.

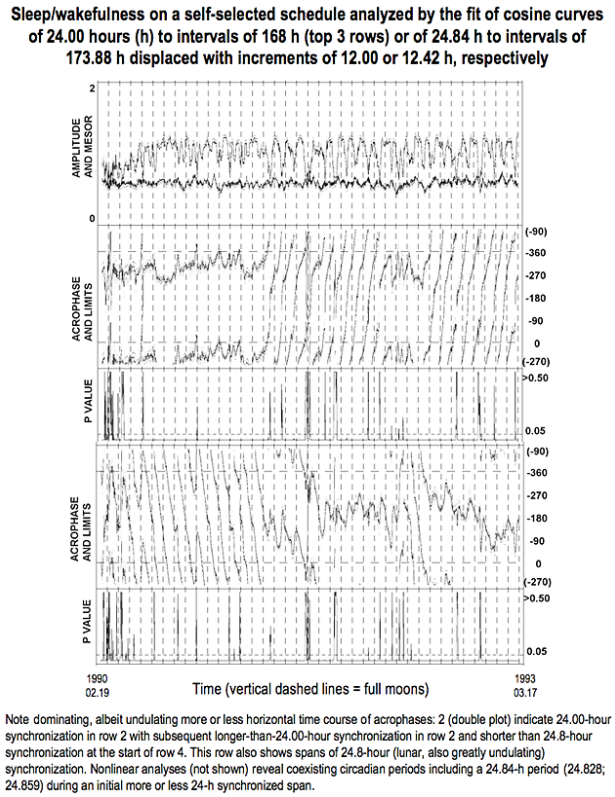


Figure 39D. Sleep-wakefulness on a self-selected schedule analyzed by the fit of cosine curves of 24.00 h to intervals of 168 h (top 3 rows) or of 24.84 h to intervals of 173.88 h displaced

with increments of 12.00 or 12.42 h, respectively. Nonlinear analyses (not shown here) reveal coexisting circadian periods including a 24.84-h period (24.828; 24.859) during an initial more or less 24-h synchronized span seen in row 2. Note, in the first 18 lunar months, in row 2, the dominating, albeit undulating and slightly delaying, not quite horizontal time course of doubly plotted acrophases indicating perhaps the interaction of a 24.00-hour schedule with a competing free-running and/or other mechanism; periods shorter than 24.8 hours are seen in the first 15 lunar months in row 4. This row also shows spans of 24.8-hour (earth tidal, also greatly undulating) synchronization. Original data from John F. Costella (66). © Halberg.

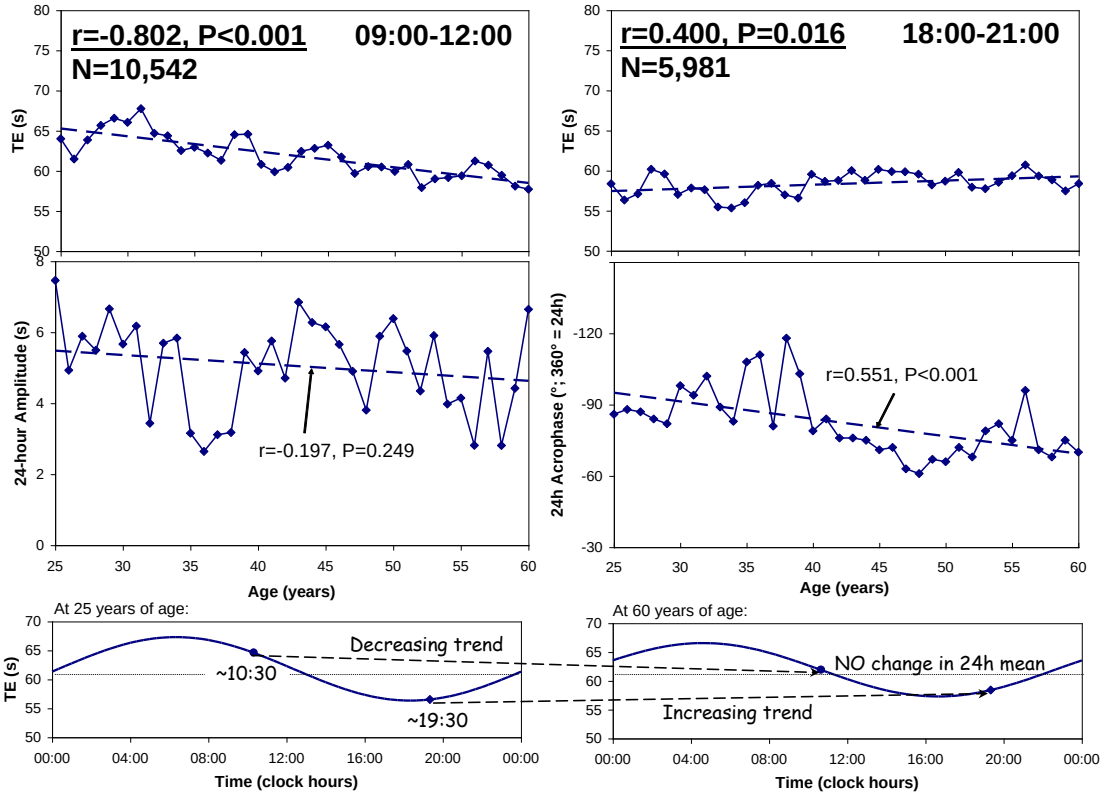


Figure 40. The data of the first and last years of 1-minute estimation by RBS were stacked along the 24-hour scale. Whereas parameter tests did not detect any change in the characteristics of the 24-hour synchronized rhythm, a paired t-test comparing eight 3-hourly mean values shows a difference ($P<0.05$). Moreover, Student's t-test on data in each of 8 equidistant bins reveal that at certain circadian stages, 1 minute passed faster in the last year than in the first year (year 35 vs. year 1). This difference was statistically significant at all test times between 06:00 and 18:00 (in some of them with $P < 0.001$), but was not found between 18:00 and 06:00, suggesting that the change in 1-minute time estimation with age is circadian stage-dependent, with highly significant differences during part of the daily active phase, but not at other circadian times. In RBS, chronomics demonstrate interaction between the circadian rhythm's stage and age. © Halberg.

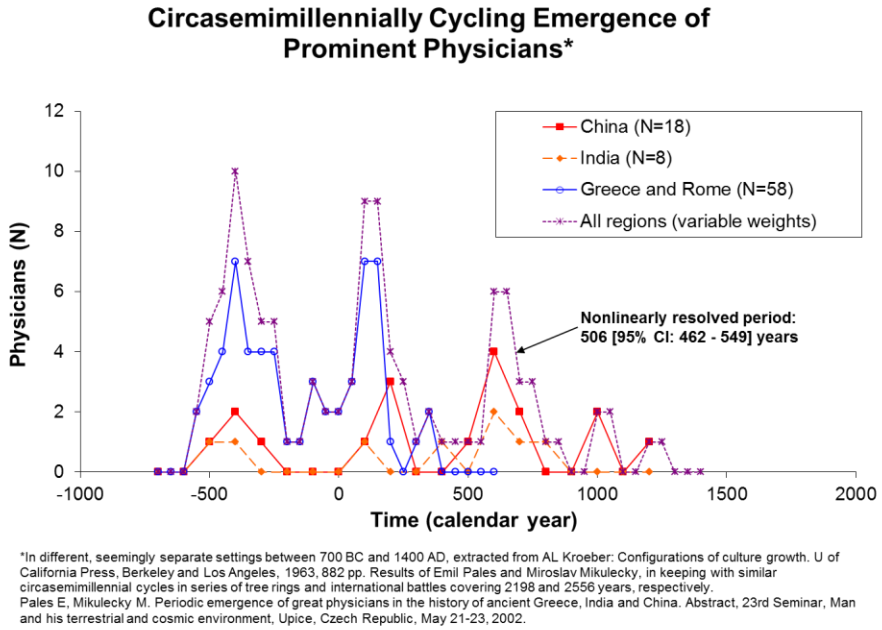


Figure 41A. About 500-year cycles in the emergence of famous physicians are visible to the naked eye, and seem to be synchronized in three completely different geographical regions among which there was originally little if any communication. © Halberg.

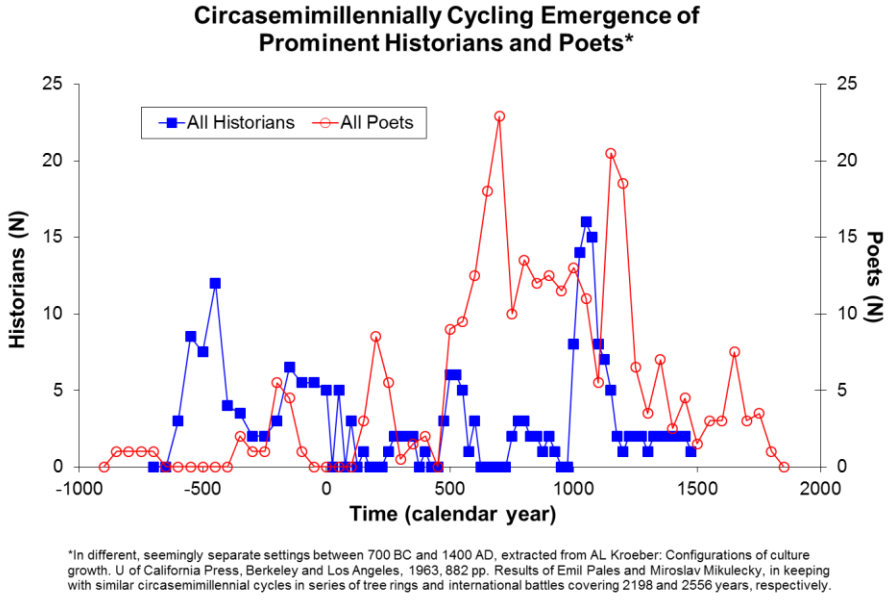


Figure 41B. About 500-year cycles are also apparent in the emergence of famous historians and poets in three completely different geographical regions among which there was originally little if any communication. © Halberg.

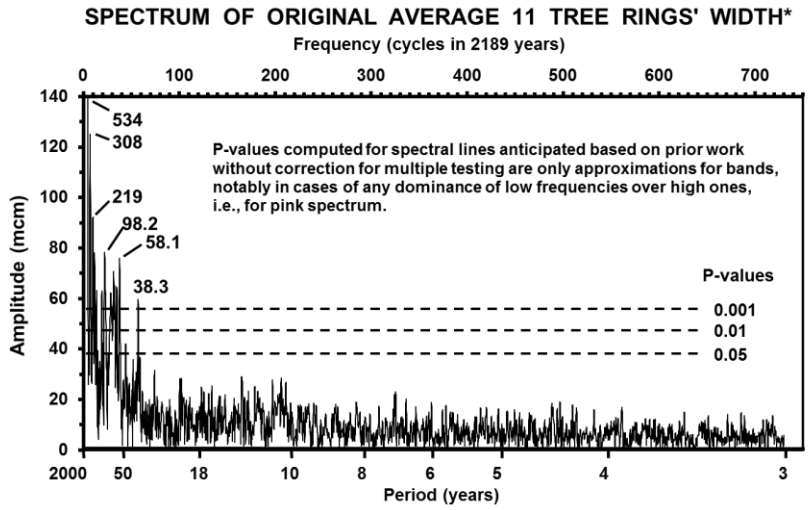


Figure 41C. Indirect proxy-approximations of solar activity via the effects of climate upon the growth of trees during spans when no other human dynamic indices exist. A cycle with a period of over 500 years here shown was obtained in the course of studies reported earlier (172). A similar cycle was also found, among others, in the spectrum of international battles (in log-transformed data) with a period of 499 years and a 95% CI extending from 459 to 539 years, as also found in human creative cultural growth by Pales and Mikulecky (145, 146) (see *Figures 41A* and *41B*). © Halberg.

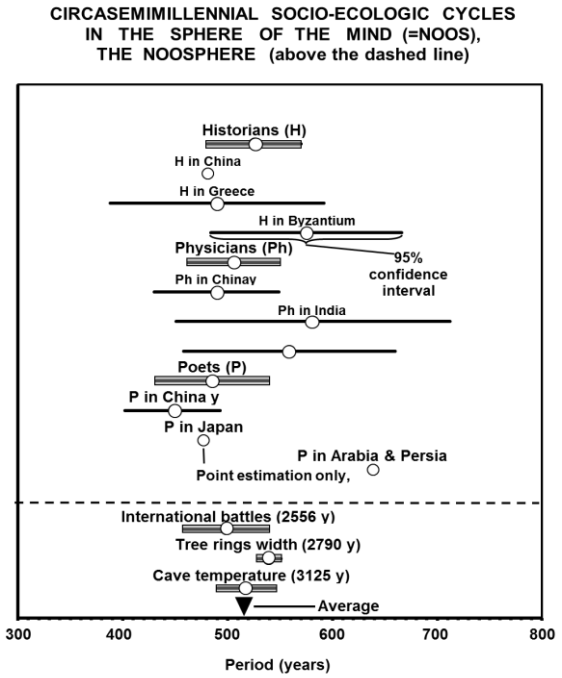


Figure 41D. Chart of about 500-year cycles in the emergence of great historians, physicians and poets, compared with similar cycles in the Wheeler index of international battles, and in two series likely related to climatic changes, namely tree ring widths and stalagmite coloring. © Halberg.

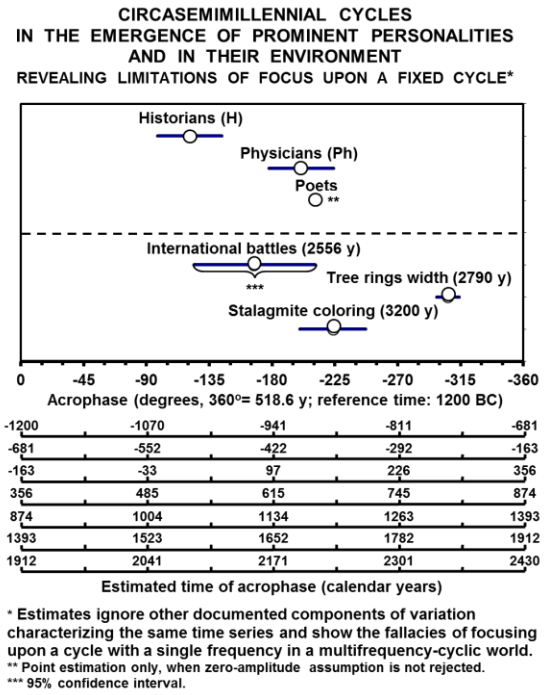


Figure 41E. Acrophase chart of about 500-year cycles shown in Figure 41D, estimated at average period. © Halberg.

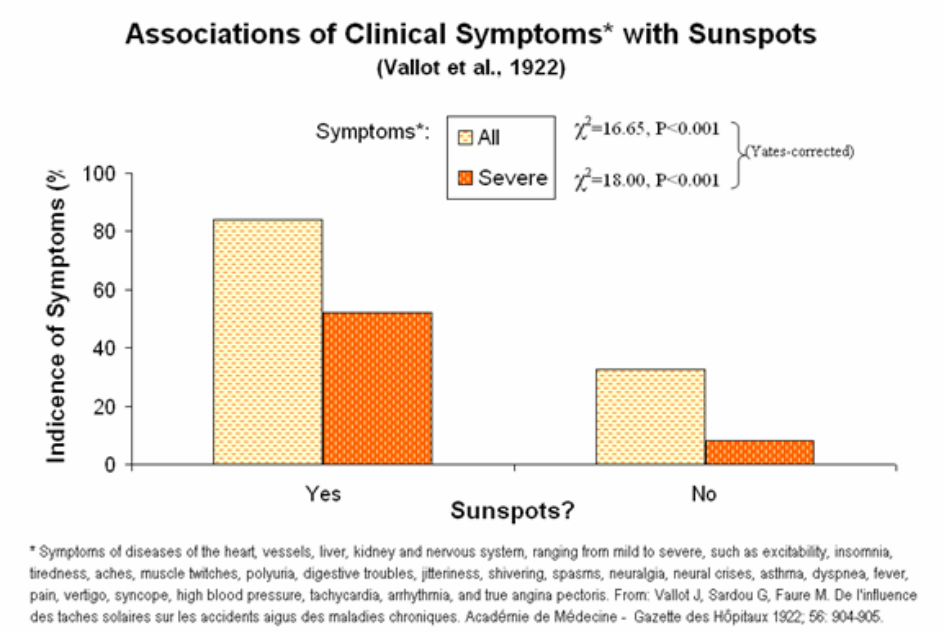


Figure 42. Meta-analysis of what Joseph Vallot, a thoughtful physicist and philanthropist, reported as an association of symptoms with solar activity over 80 years ago. Even mild symptoms, such as excitability, insomnia, tiredness, aches, muscle twitches, etc., have long been associated with sunspots (173). We stand on the shoulders of many others who noted a lead in phase by a day of symptoms vs. sunspots. © Halberg.

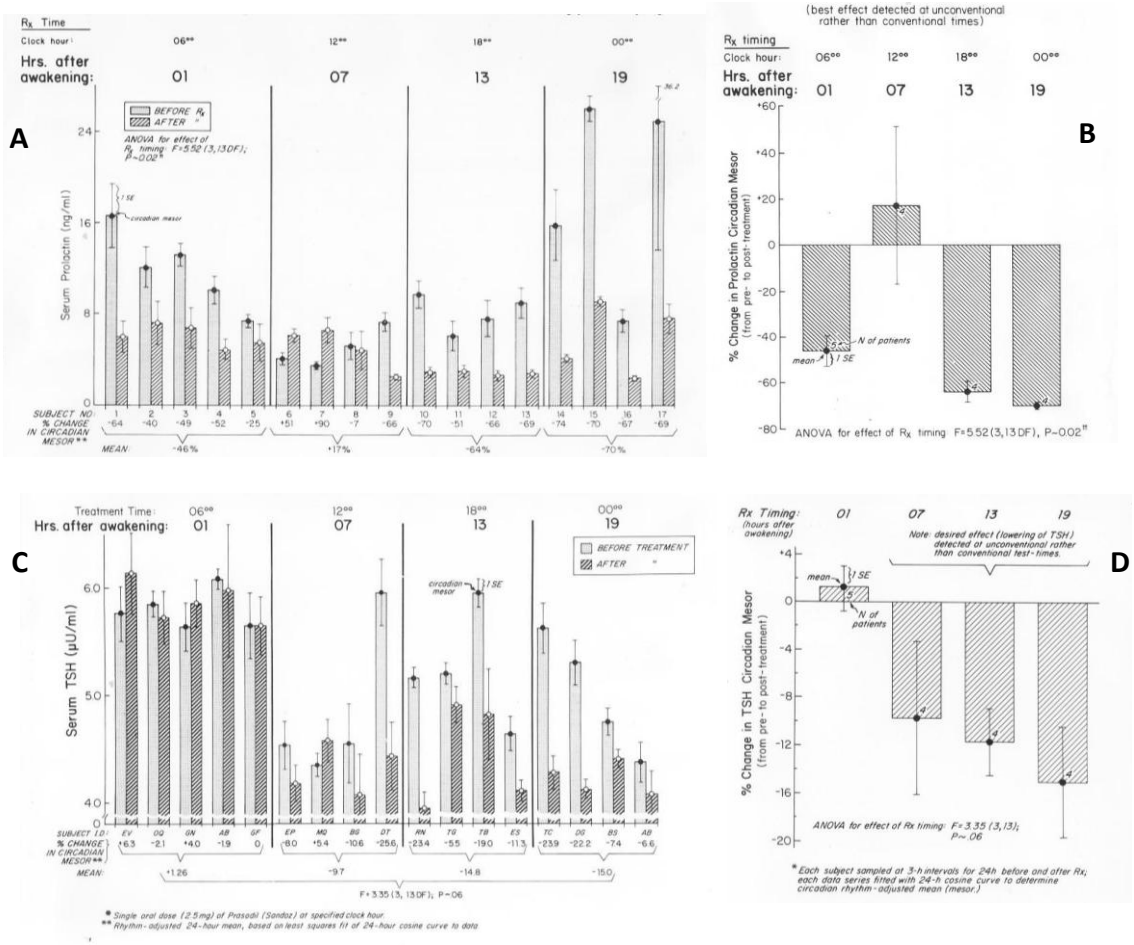


Figure 43. Circadian stage-dependence of effect of bromocriptine mesylate on circulating prolactin (A-B) and TSH (C-D) of patients with prostatic hypertrophy. Individual responses of patients at one of four different circadian stages are shown on the left. A summary by one-way analysis of variance (right) indicates that the treatment was effective in lowering prolactin when given at 1, 13, and 19 h after awakening, but not at 7 h after awakening. Likewise, the treatment was more effective in lowering TSH at 13 and 19 h than at 7 h after awakening, and it was not effective at 1 h after awakening. © Halberg.

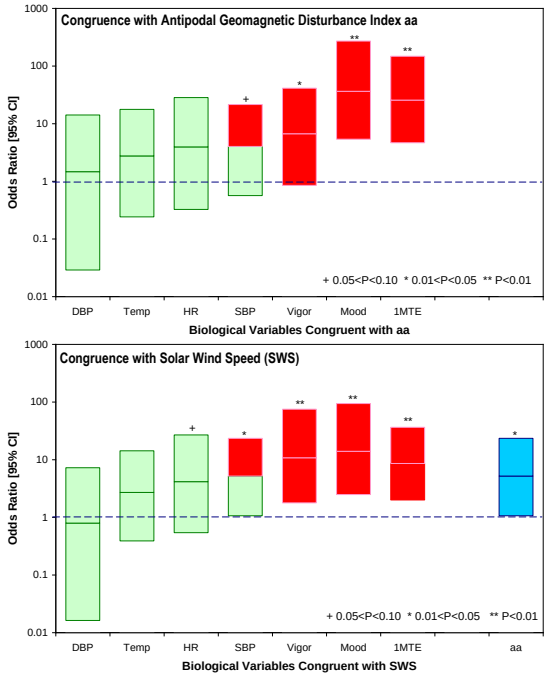


Figure 44. By the criterion of the number of shared frequencies (with overlapping 95% confidence intervals), odds ratios of human mental functions vs. geomagnetics (top) or vs. interplanetary magnetism (bottom) more than match the accepted association of geo- and interplanetary magnetism (blue). © Halberg.

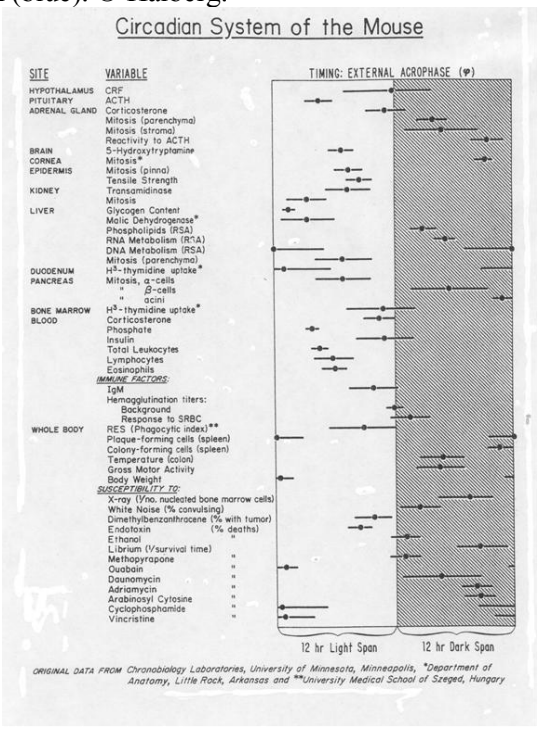
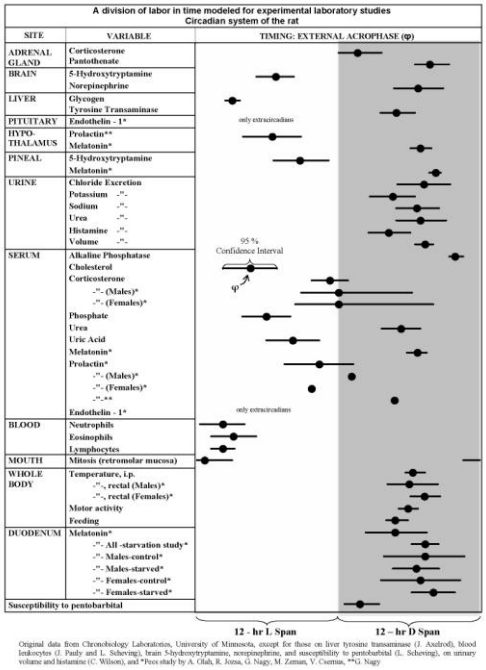
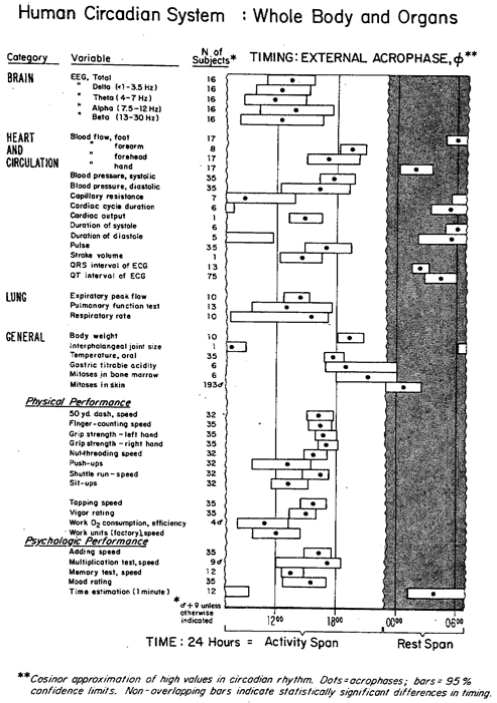


Figure 45A. Phase chart. Circadian system of the mouse. Note differences in phase as a division of labor in time. © Halberg.



Original data from Chronobiology Laboratories, University of Minnesota, except for those on liver tyrosine transaminase (J. Axelrod), blood leukocytes (J. Pauly and L. Scheving), brain 5-hydroxytryptamine, norepinephrine, and susceptibility to pentobarbital (L. Scheving), on urinary volume and histamine (C. Wilson), and *Pross study by A. Olah, R. Jozsa, G. Nagy, M. Zeman, V. Csernus, **G. Nagy

Figure 45B. Phase chart. Circadian system of the rat. Note differences in phase as a division of labor in time. © Halberg.



** Cosinor approximation of high values in circadian rhythm. Dots = acrophases; bars = 95 % confidence limits. Non-overlapping bars indicate statistically significant differences in timing.

Figure 45C. Phase chart. Human circadian system. Note differences in phase as a division of labor in time. © Halberg.

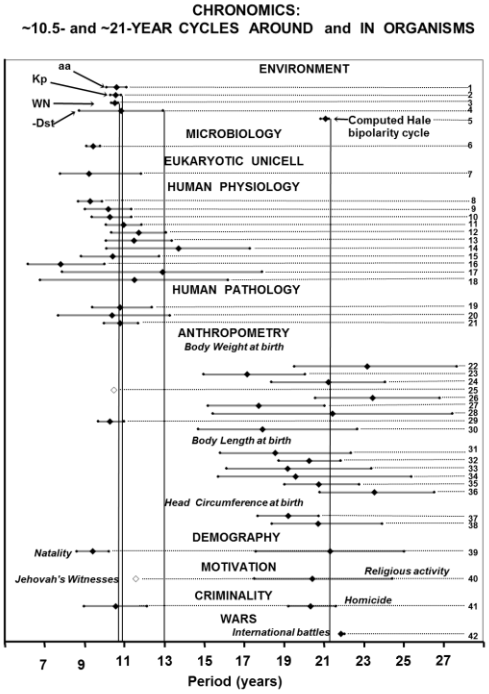


Figure 45D. Period chart. Human decadal-didecadal system. © Halberg.

Chronomics: ~10.5- and ~21-year cycles in and around us

				Period (years)						
				Lower limit*	**Best Fit**	Upper limit*	Series duration Dates	Years	Number of data	Geographic site
	Line									
Environment	1	aa = Antipodal Geomagnetic Index		10.12	**10.63**	11.13	1890-1999	110	1 / year	
	2	Kp = Planetary Geomagnetic disturbance		10.32	**10.58**	10.85	1932-1999	68	1 / month	
	3	WN = Wolf relative sunspot number		10.37	**10.54**	10.70	1890-1999	110	1 / year	
	4	-Dst = Equatorial geomagnetic disturbance		8.75	**10.85**	12.96	1973-1999	27	"	
				10.48	**10.51**	10.55	1700-1999	300	"	
	5	Bipolarity "Hale Cycle" **		20.86	**21.10**	21.26	1890-1999	110	"	
				21.42	**21.428**	21.43	1700-1999	300	"	
Biology	6	Prokaryotes: Air Bacterial Sectoring		9.12	**9.45**	9.81	1970-1982	13	3,744	Italy
	7	Eukaryotes: Unicellular Algal O_2 Production		7.79	**9.24**	11.87	1980-1991	11	324	Germany
Physiology* **	8	Mood (RBS)		10.11	**11.50**	13.41	1966-1998	33	~5 / day	USA
	9	Time (1-Minute) Estimation (RBS)		9.38	**10.29**	11.37	1966-1998	33	"	"
	10	Urinary 17-ketosteroid excretion (CH)		8.70	**9.30**	9.90	1948-1963	15	1 / day	Denmark
	11	Peak Expiratory Flow (RBS)		10.36	**11.74**	13.11	1966-1998	33	~5 / day	USA
	12	Respiratory Rate (RBS)		10.13	**12.50**	17.32	1966-1998	33	"	"
	13	Systolic Blood Pressure - SBP (RBS)		9.05	**10.21**	11.36	1966-1998	33	"	"
	14	Standard Deviation of SBP (YW)		8.85	**10.43**	12.76	1987-1998	11	~48 / day	Japan
	15	Diastolic Blood Pressure - DBP (RBS)		10.09	**10.98**	11.87	1966-1998	33	~5 / day	USA
	16	Standard Deviation of DBP (YW)		6.18	**7.82**	10.02	1987-1998	11	~48 / day	Japan
	17	Heart Rate - HR (YW)		9.54	**12.93**	17.91	1987-1998	11	"	"
	18	Standard Deviation of HR (YW)		8.27	**11.52**	16.22	1987-1998	11	"	"
Pathology	19	Myocardial Infarction		10.00	**10.80**	11.70	1960-1996	37	129,205	USA
	20	Leptospirosis		9.40	**10.80**	12.40	1949-1995	47	2,907	Slovakia
	21	Diabetes		7.70	**10.40**	13.30	1985-1995	11	1,369	"
Anthropo-		***Body Weight***	***Boys***							
metry	22		Minnesota	19.53	**23.19**	27.67	1963-1998	36	2,136,745	USA
at birth	23		Alma-Ata Russians	14.99	**17.17**	20.07	1946-1998	53	9,056	Kazakhstan
	24		" Kazakhs	18.39	**21.24**	24.05	1946-1998	53	3,459	"
	25		Moscow		**10.49**		1874-1985	112	5,987	Russia
			Girls							
	26		Minnesota	20.58	**23.46**	26.83	1963-1998	36	1,039,464	USA
	27		Alma-Ata Russians	15.21	**17.75**	21.06	1946-1998	53	9,105	Kazakhstan
	28		" Kazakhs	15.44	**21.45**	27.45	1946-1998	53	3,448	"
	29		Moscow	9.70	**10.29**	11.01	1874-1985	112	5,840	Russia
			Both genders							
	30		Denmark	14.71	**17.94**	22.68	1973-1994	22	1,166,206	Denmark
		Body Length	***Boys***							
	31		Alma-Ata Russians	15.82	**18.58**	22.38	1946-1998	53	9,026	Kazakhstan
	32		Moscow	18.76	**20.28**	21.86	1874-1985	112	5,976	Russia
			Girls							
	33		Alma-Ata Russians	16.13	**19.20**	23.39	1946-1998	53	9,105	Kazakhstan
	34		" Kazakhs	15.72	**19.60**	25.40	1946-1998	53	3,485	"
	35		Moscow	19.05	**20.76**	22.78	1874-1985	112	5,976	Russia
			Both genders							
	36		Denmark	20.81	**23.55**	26.55	1973-1994	22	1,166,206	Denmark
		Head Circumference								
	37		***Boys*** Moscow	17.71	**19.23**	20.75	1874-1985	112	5,976	Russia
	38		***Girls*** "	18.42	**20.73**	23.95	1874-1985	112	5,820	"
Demography	39	Birth rate		8.63	**9.43**	10.23	1940-1996	57	57	USA
				17.61	**21.33**	25.05	1940-1996			
Motivation	41	Religious activity of Jehovah's Witnesses		17.52	**20.44**	24.45	1950-1999	50	328,572[#]	Worldwide
									5,653,987[##]	
Criminality	40	Homicide		8.99	**10.58**	12.16	1900-1998	99	99	USA
				19.23	**20.35**	21.62				
Wars	42	International battles		21.87	**21.96**	22.06	599BC-1957	2556	2556	Worldwide

* 95% confidence limit; not shown if cycle is not statistically significant.
** Computed by changing the sign of WN at each WN minimum.
***RBS - Dr. Robert B. Sothern, CH - Dr. Christian Hamburger, YW - Dr. Yoshihiko Watanabe.
[#] in 1950, [##] in 1999, pool of 103 plus other unspecified number of sites.

Figure 45E. Key to period chart. Human decadal-didecadal system. © Halberg.

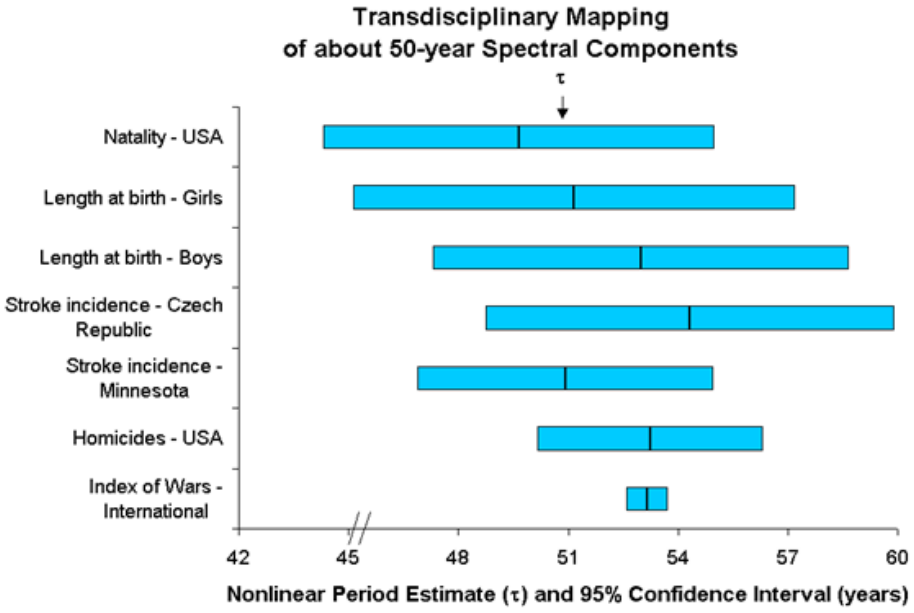


Figure 46. Period chart. Human semicentennian system. © Halberg.

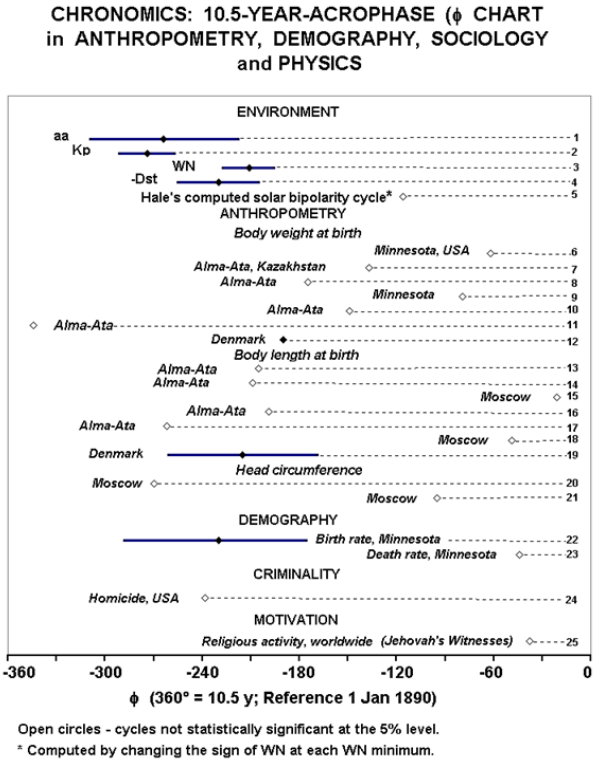


Figure 47A. Human decadal phase chart. © Halberg.

Chronomics: Acrophases of 10.5-year cycles in and around us

	Line		Acrophase (degrees) Lower limit*	Point estimate	Upper limit*	Series duration Dates	Years	Number of data	Geographic site
Environment	1	aa = Antipodal Geomagnetic Index	-218	**-264**	-309				
	2	Kp = Planetary Geomagnetic disturbance	-257	**-274**	-291	1932-1999	68	1 / month	
	3	WN = Wolf relative sunspot number	-196	**-211**	-227	1890-1999	110	1 / year	
	4	-Dst = Equatorial geomagnetic disturbance	-205	**-230**	-255	1973-1999	27	1 / year	
	5	Bipolarity "Hale Cycle" **		**-116**		1890-1999	110	1 / year	
Anthropo-metry at birth		***Body Weight*** ***Boys***							
	6	Minnesota		**-62**		1963-1998	36	2,136,745	USA
	7	Alma-Ata Russians		**-137**		1946-1998	53	9,056	Kazakhstan
	8	" Kazakhs		**-175**		1946-1998	53	3,459	"
		Girls							
	9	Minnesota		**-79**		1963-1998	36	1,039,464	USA
	10	Alma-Ata Russians		**-149**		1946-1998	53	9,105	Kazakhstan
	11	" Kazakhs		**-344**		1946-1998	53	3,448	"
		Both genders							
	12	Denmark		**-190**		1973-1994	22	1,166,206	Denmark
		Body Length ***Boys***							
	13	Alma-Ata Russians		**-205**		1946-1998	53	9,026	Kazakhstan
	14	" Kazakhs		**-209**		1946-1998	53	3,325	"
	15	Moscow		**-21**		1874-1985	112	5,976	Russia
		Girls							
	16	Alma-Ata Russians		**-199**		1946-1998	53	9,105	Kazakhstan
	17	" Kazakhs		**-262**		1946-1998	53	3,485	"
	18	Moscow		**-49**		1874-1985	112	5,976	Russia
		Both genders							
	19	Denmark	-169	**-215**	-261	1973-1994	22	1,166,206	Denmark
	20	***Head Circumference***							
		Boys Moscow		**-270**		1874-1985	112	5,976	Russia
	21	***Girls*** "		**-95**		1874-1985	112	5,820	"
Demography	22	Birth rate	-176	**-230**	-288	1940-1996	57	57	USA
	23	Death rate		**-44**		1940-1996	57	57	"
Criminality	24	Homicide		**-238**		1900-1998	99	99	"
Motivation	25	Religious activity of Jehovah's Witnesses		**-38**		1950-1999	50	328,572[s] 5,653,987[ss]	Worldwide

* 95% confidence limit; not shown if cycle is not statistically significant. ** Computed by changing the sign of WN at each WN minimum.
[s] in 1950, [ss] in 1999, pool of 103 plus other unspecified number of sites.

Figure 47B. Key to human decadal phase chart. © Halberg.

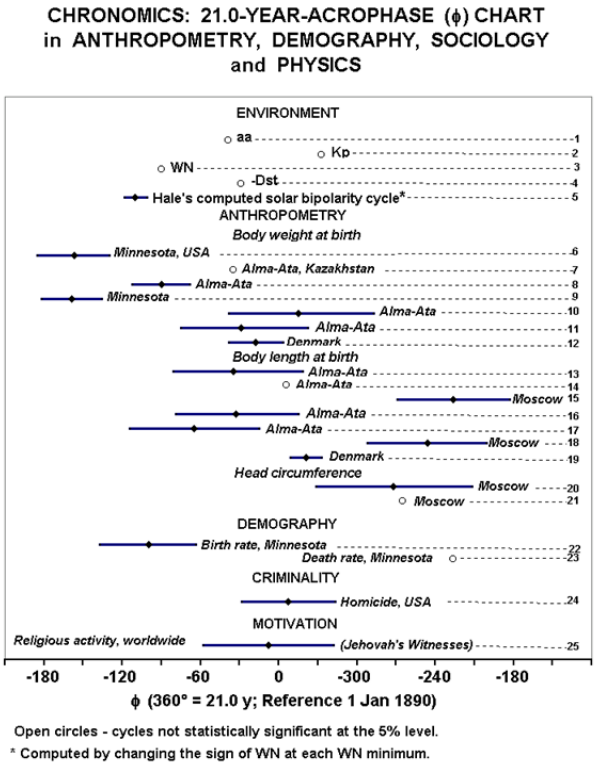


Figure 47C. Human didecadal phase chart. © Halberg.

Chronomics: Acrophases of 21.0-year cycles in and around us

	Line			Acrophase (degrees) Lower limit*	Point esti-mate	Upper limit*	Series duration Dates	Years	Number of data	Geographic site
Environment	1	aa = Antipodal Geomagnetic Index			**-39**					
	2	Kp = Planetary Geomagnetic disturbance			**-327**		1932-1999	68	1 / month	
	3	WN = Wolf relative sunspot number			**-90**		1890-1999	110	1 / year	
	4	-Dst = Equatorial geomagnetic disturbance			**-29**		1973-1999	27	1 / year	
	5	Bipolarity "Hale Cycle" **		-101	**-110**	-118	1890-1999	110	1 / year	
Anthropo-metry at birth		***Body Weight***	***Boys***							
	6		Minnesota	-130	**-157**	-185	1963-1998	36	2,136,745	USA
	7		Alma-Ata Russians		**-35**		1946-1998	53	9,056	Kazakhstan
	8		" Kazakhs	-68	**-90**	-112	1946-1998	53	3,459	"
			Girls							
	9		Minnesota	-136	**-159**	-182	1963-1998	36	1,039,464	USA
	10		Alma-Ata Russians	-287	**-345**	-38	1946-1998	53	9,105	Kazakhstan
	11		" Kazakhs	-338	**-29**	-75	1946-1998	53	3,448	"
			Both genders							
	12		Denmark	-357	**-18**	-38	1973-1994	22	1,166,206	Denmark
		Body Length	***Boys***							
	13		Alma-Ata Russians	-342	**-35**	-81	1946-1998	53	9,026	Kazakhstan
	14		" Kazakhs		**-354**		1946-1998	53	3,325	"
	15		Moscow	-183	**-226**	-269	1874-1985	112	5,976	Russia
			Girls							
	16		Alma-Ata Russians	-345	**-33**	-79	1946-1998	53	9,105	Kazakhstan
	17		" Kazakhs	-15	**-65**	-114	1946-1998	53	3,485	"
	18		Moscow	-201	**-246**	-292	1874-1985	112	5,976	Russia
			Both genders							
	19		Denmark	-327	**-339**	-351	1973-1994	22	1,166,206	Denmark
	20	***Head Circumference***								
			Boys Moscow	-212	**-272**	-331	1874-1985	112	5,976	Russia
	21		***Girls*** "		**-265**		1874-1985	112	5,820	"
Demography	22	Birth rate		-64	**-100**	-137	1940-1996	57	57	USA
	23	Death rate			**-226**		1940-1996	57	57	"
Criminality	24	Homicide		-317	**-353**	-28	1900-1998	99	99	"
Motivation	25	Religious activity of Jehovah's Witnesses		-318	**-8**	-58	1950-1999	50	328,572# 5,653,987##	Worldwide

* 95% confidence limit; not shown if cycle is not statistically significant.
** Computed by changing the sign of WN at each WN minimum.
# in 1950, ## in 1999, pool of 103 plus other unspecified number of sites.

Figure 47D. Key to human didecadal phase chart. © Halberg.

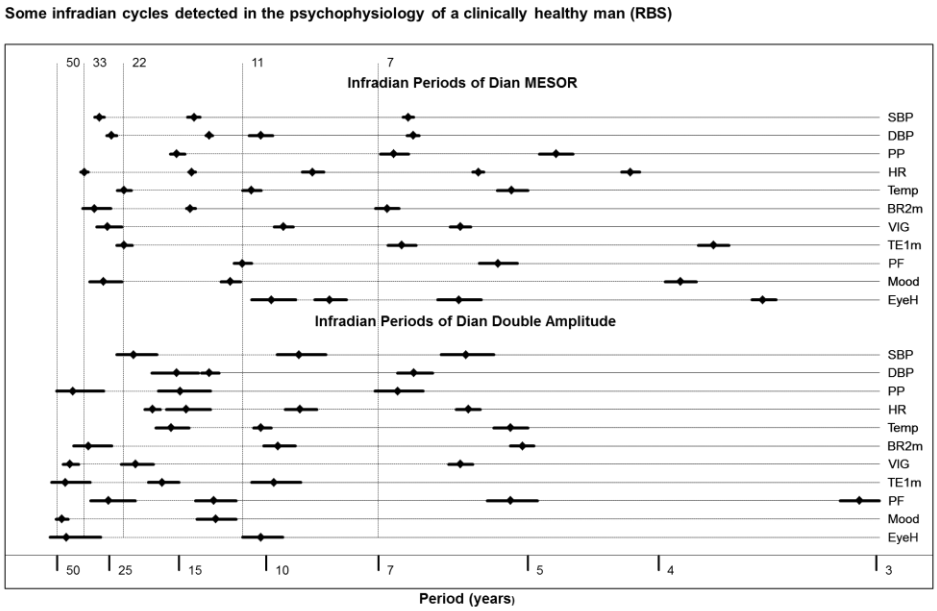


Figure 48. Partial infradian period chart of aspects of the psychophysiology of a healthy man (RBS). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PP: Pulse Pressure; HR: Heart Rate; Temp: Oral Temperature; BR2m: Breathing Rate (2 minutes); VIG: self-rated Vigor; TE1m: 1-minute Time Estimation; PF: Peak (Expiratory) Flow; Mood: self-rated Mood; EyeH: Eye-hand coordination; horizontal bars are 95% confidence intervals of nonlinearly estimated periods. © Halberg.

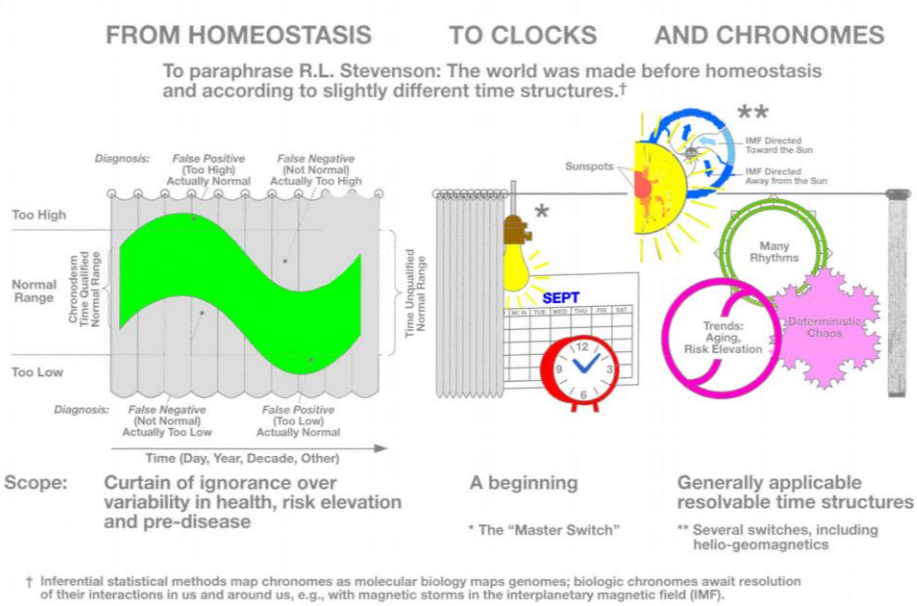


Figure 49A. Concepts like homeostasis represent an excuse for a curtain of ignorance closed over the range of physiological variation. Clocks and calendars (middle) open that curtain only partly, ignoring structures consisting of deterministic and other chaos, trends and the many rhythms other than circadian and circannual components in and around us and thus are no substitute for mapped coperiodisms (right) in the biosphere and its environment, *Figure 49B*. © Halberg.

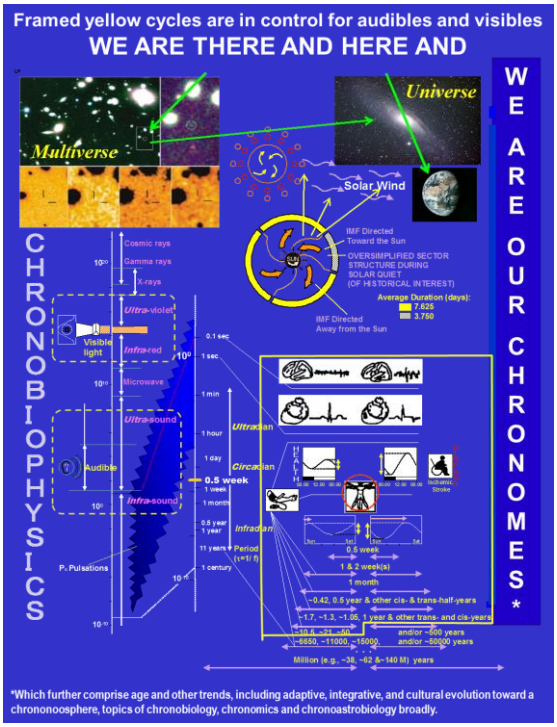


Figure 49B. Multifrequency cycles in us and around us. Biological cycles tend to have environmental counterparts. Some cycles detected in biology prompted their discovery in the environment. © Halberg.

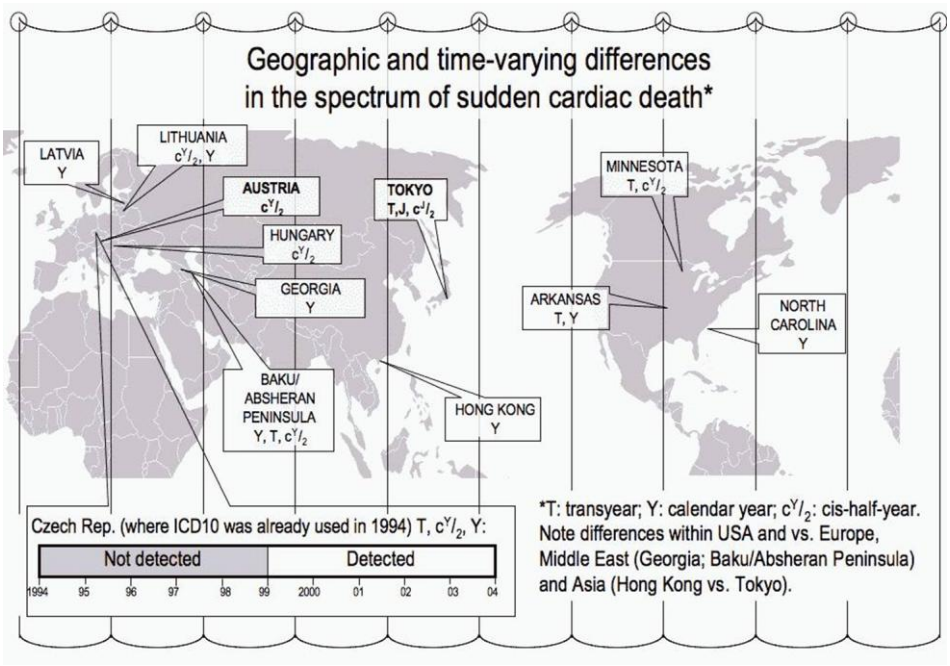


Figure 50. Need for a global and local (glocal) approach in space and time illustrated by incidence pattern in sudden cardiac deaths varying with time. A transyear is found in Minnesota with a cis-half-year (cY/2) and both a calendar year and a transyear in Arkansas and the Czech Republic, where a cis-half-year, corresponding in length to an also-transient period of hard solar flares, is detected after but not before 1999. © Halberg.

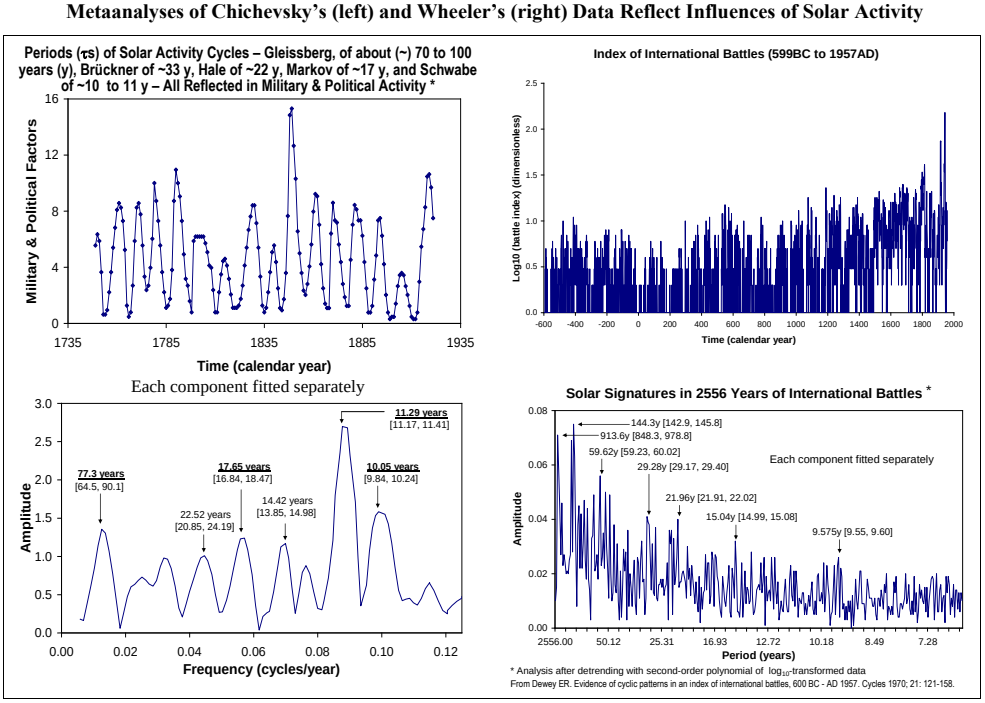


Figure 51A. Solar periodicities of Chizhevsky's (left) and Wheeler's (right) data (top half) mirrored in our meta-analyses (bottom half). © Halberg.

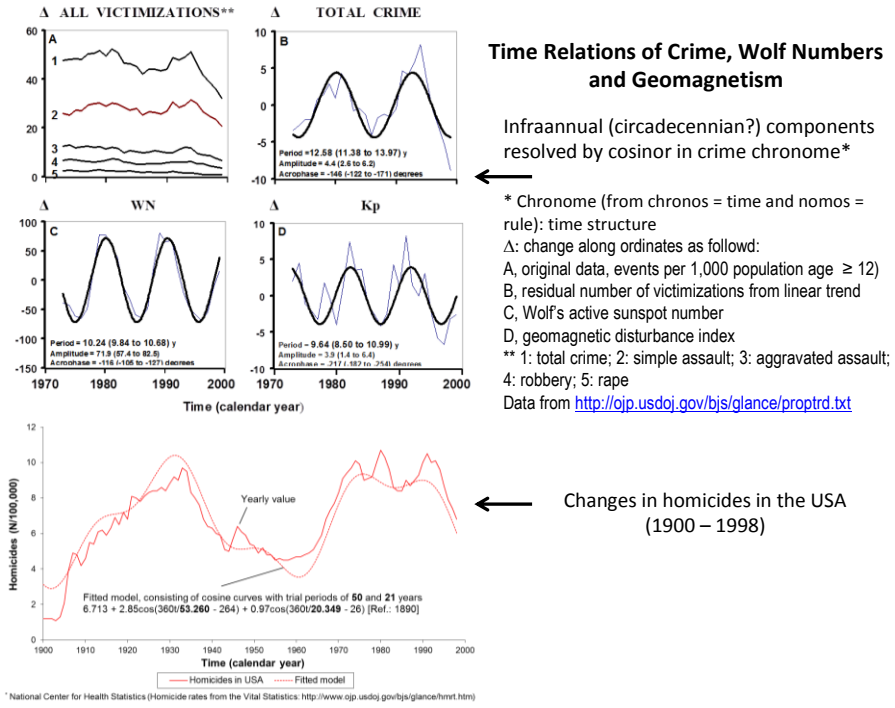


Figure 51B. About (~) 10-yearly (top and middle) and ~50- and 20-yearly (bottom) periods in the "bad" ("morbidity") of society (174). © Halberg.

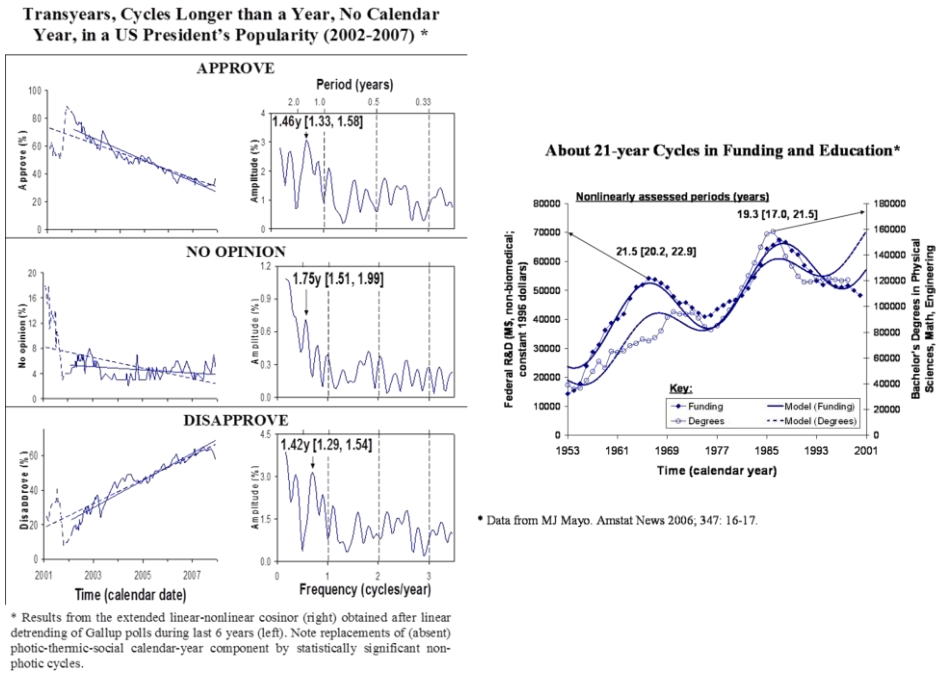


Figure 51C. The prominence of the magnetic transyears over the calendar year in presidential politics (left) and of a near 20-year cycle of sunspot bipolarity in the funding of non-medical (Defense Department-related) education are in keeping with an association with space weather. © Halberg.

About 21.0-year Cycle in Proselytism: data from all locations (upper left) and least squares spectrum (bottom left); parameters (upper middle and right) and their resolution (bottom middle and right) correlate with geographic/geomagnetic latitude

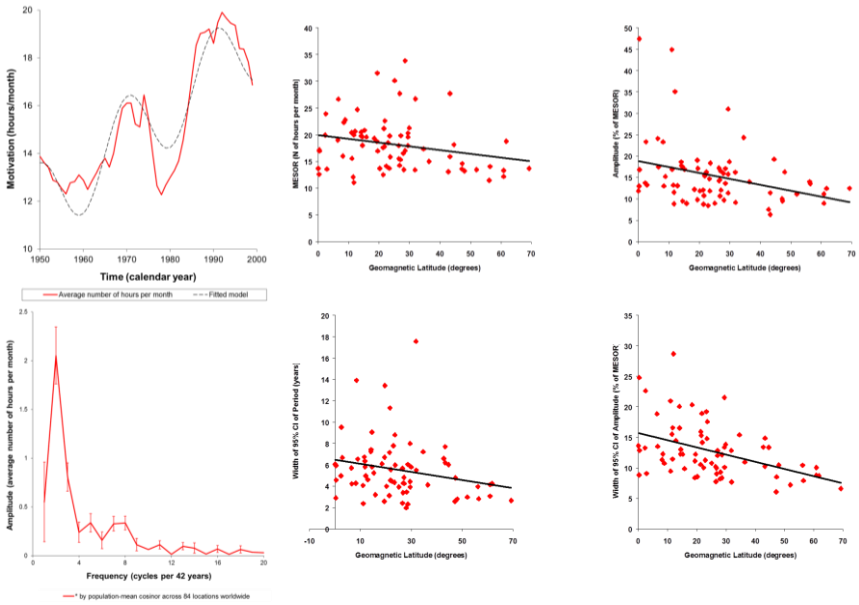


Figure 51D. An approximation of the very hard-to-gauge desire to do "good": proselytism of Jehovah's Witnesses mirrored in the ~21-year Hale cycle (left) with cycle's parameters influenced geomagnetically (175). © Halberg.

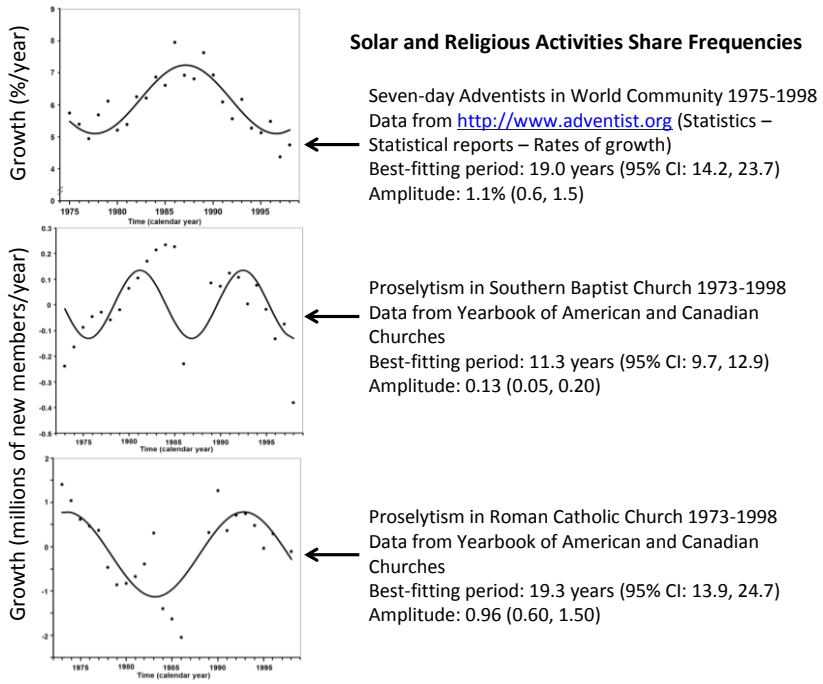


Figure 51E. Another approximation of the very hard-to-gauge desire to do "good": the ~21-year Hale sunspot bipolarity cycle (top and bottom) and the ~11-year Horrebow-Schwabe sunspot number cycle (middle) are mirrored in religion ("good" activities), their length being covered by the 95% confidence intervals of the periods given in ( ). © Halberg.

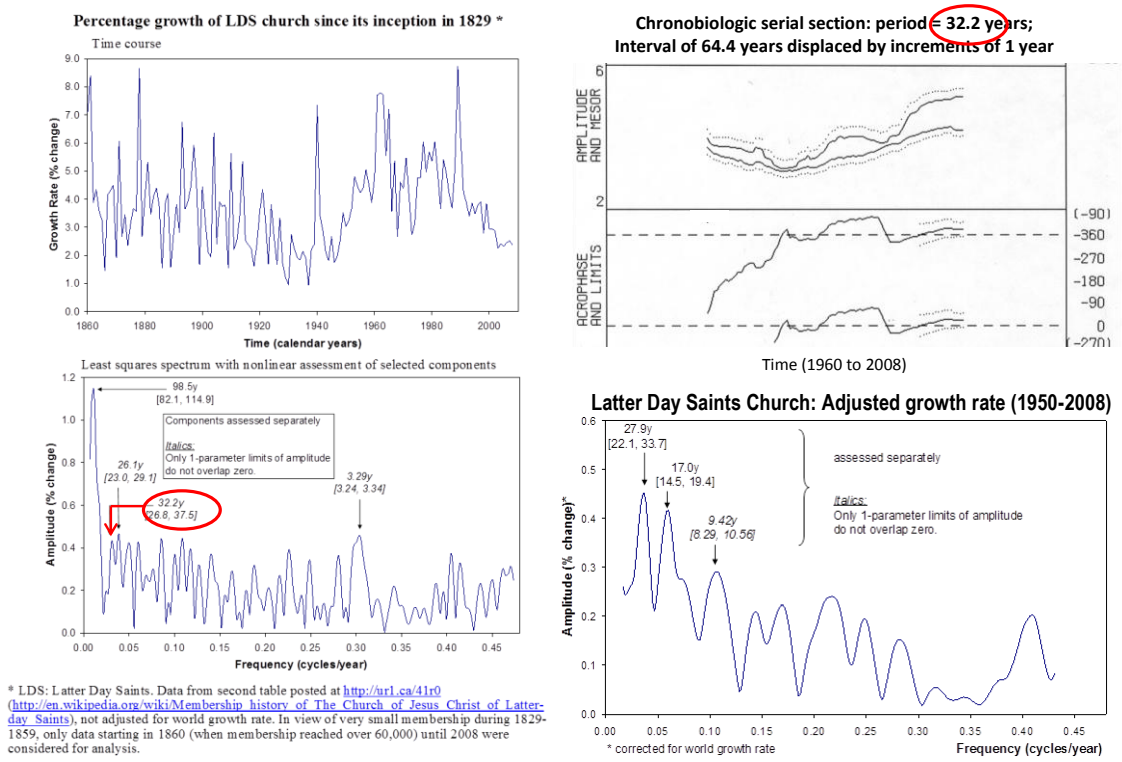


Figure 51F. A third approximation of the very hard-to-gauge desire to do "good": an aeolian Brückner-Egeson-Lockyer (BEL) paratridecadal cycle, apparent in a spectrum of data from 1860 on (left) becomes more prominent during the end of the record, as seen in a chronomic serial section by the difference between the two curves (top right) describing the BEL amplitude that increases with time, and during that span several components are nonlinearly resolved, congruent with solar activity cycles, the latter not shown. © Halberg.

Figures 52A-O (overall). Cross-validation by cycles in space weather and glocal technique of analysis gradually refines the infradian window of steroid dynamics. A for-us unique time series with few gaps covering 15 years of daily 17-ketosteroid determinations, the analysis of which has been steadily improved over the past half century, resulting in a map of cycles complementing the circadian system and allowing a first view of a bushel basket of novel infradians (with periods longer than 28 hours). On the clinical side, if recognized they can forestall androgen substitution therapy when it is not necessary (in the case examined herein, CH, they did not prevent his androgen use because the numerical analyses were retrospective). There is, of course, other applied and basic interest in learning how the cosmos influences our physiology, as a reference for also-documented pathology, perhaps in part through steroidal mechanisms, *Figure 15*.

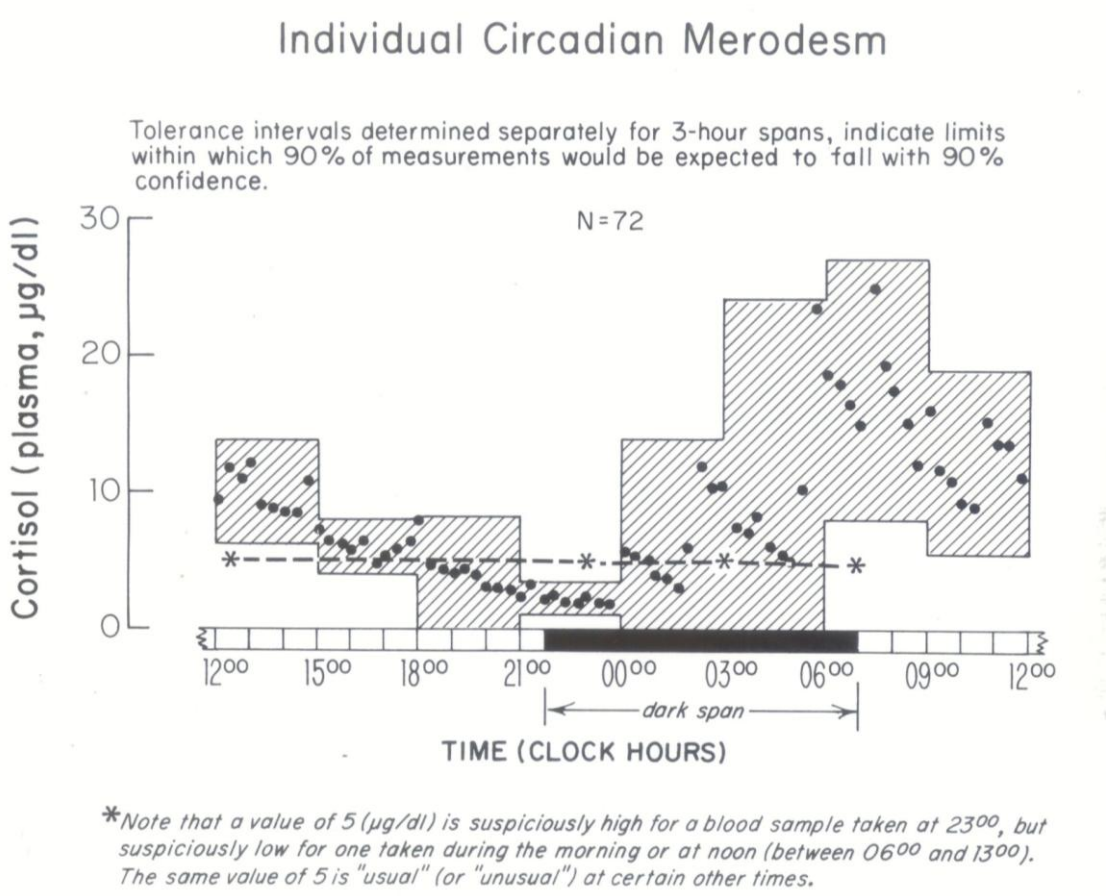


Figure 52A. Didactic demonstration.Variations of circulating corticoid and other hormones can be mapped in the saliva of an individual (*Figure 15*). It is worthwhile nonetheless to illustrate a personalized chart of a range of acceptable values for time-specified single plasma cortisol samples, a desideratum half a century ago (individual circadian merodesm). Tolerance intervals determined separately for 3-hour spans indicate limits within which 90% of measurements would be expected to fall with 90% confidence. On the sleep schedule depicted by a black horizontal bar on the abscissa, a cortisol value such as 5 µg/dl (asterisk) may be too low at one time (e.g., 06:30), too high at another time (e.g., 23:00), or normal at still another time (e.g., 03:00). But at a time when over 11,700 hormone assays could be completed on a motivated subject, reliance on saliva rather than blood and on rhythm characteristics rather than spotchecks can be advocated. © Halberg.

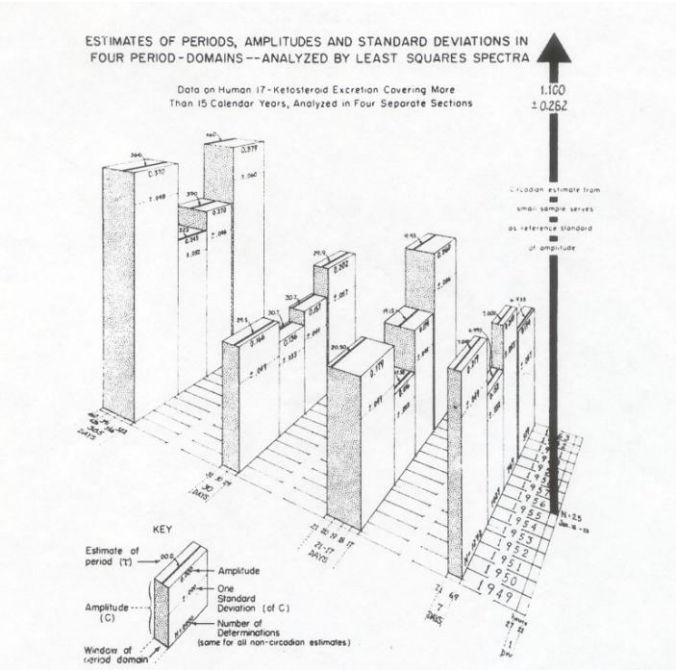


Figure 52B. In the 1960s, we obtained a 5-day series of 4 consecutive 4-hourly and one 8-hourly urine sample/day and a 15-year-long series (with gaps) of daily 17-ketosteroid (KS) excretion by a clinically healthy man, CH. While KS are unspecific, they estimate, among others, the breakdown products of steroids and may convey some aspects of variability in corticosteroids. In the 5-day series, a prominent circadian component is shown by an arrow. In addition, there were much smaller peaks at many frequencies, some of which, admittedly arbitrarily chosen, were studied by cosinor in 4 sections of the 15-year series. Data analyzed were from days when the subject did not self-administer androgen suppositories. Infradian results appeared to be roughly reproducible from one subspan to the next to the unaided eye, an interpretation revised by further analyses. © Halberg.

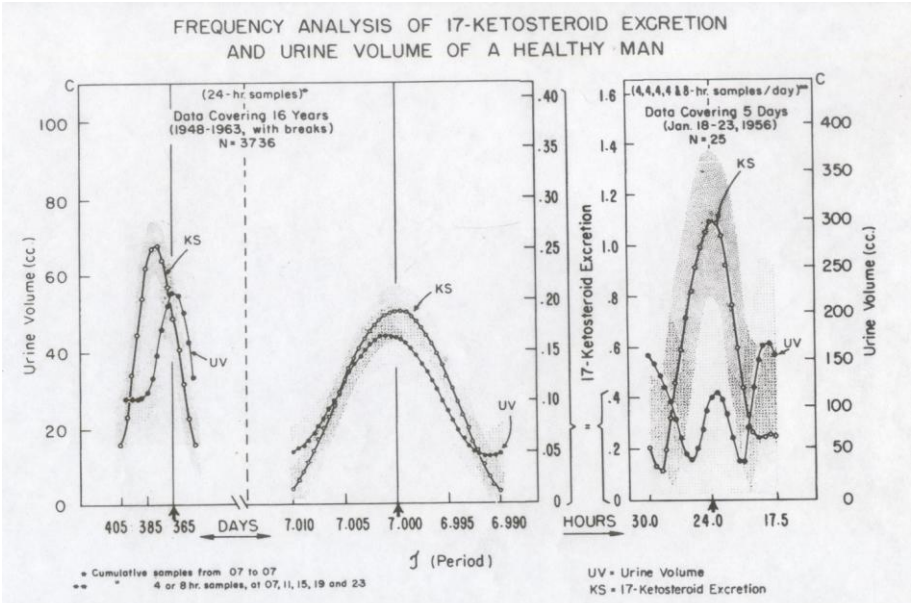


Figure 52C. Three windows were singled-out for further analyses: a 24-h synchronized major

component (right) stands out prominently, overshadowing the corresponding minor peaklet in urine volume, in which the KS were determined. Before looking at the about (~) yearly component (left) and an ~weekly component (middle), a change in scale must be kept in mind, as shown by brackets between the windows in the middle and on the right. With this qualification as to their magnitude ("minitude"?), there are peaks in both KS and urine volume (UV) in the circannual region (left), with the urine volume peak, but not that in KS peak synchronized to the calendar year: the KS peak is clearly distant from the precise year length. Both KS and UV seem to be overall synchronized by the societal week (middle). © Halberg.

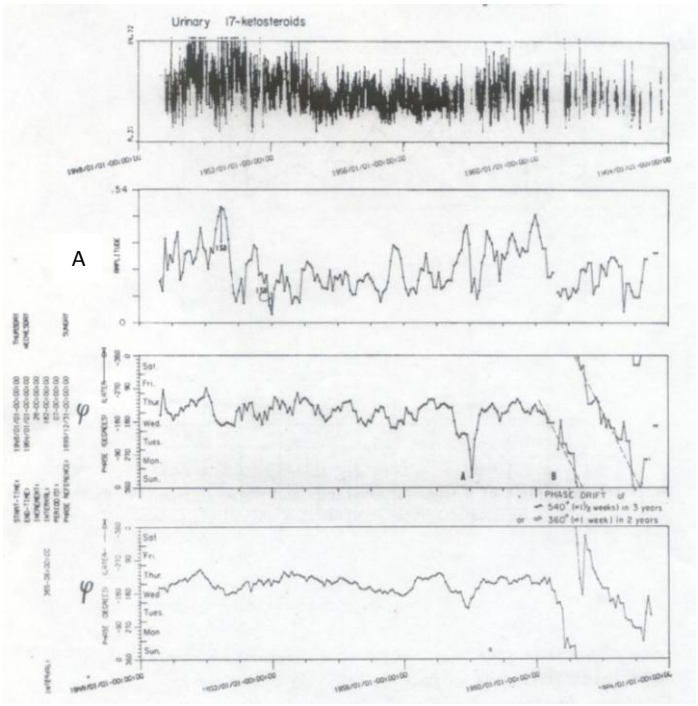


Figure 52D. The window of the weekly (circaseptan) region is complemented by a chronobiologic serial section that shows the original data of the long KS series in the top row. Without time series analyses, the unaided eye sees ups and downs in the data but can guesstimate neither the precise periodicities in the infradian domain of the time structure of the series nor any CIs (95% confidence intervals) of the periods, τs. These aeolian components are nonstationary and best assessed with an approximation of their uncertainties. The second row summarizes the time course of changes in the circaseptan extent of change, the amplitude, A, with two vertical lines, labeled SD, being indications of the length of the standard deviation of A. The unaided eye can now detect more clearly than in the top row, high values for the extent of the weekly swing, if not clear peaks about 9 or 10 years apart, possibly a circadecennian modulation of the circaseptan amplitude. It is certainly unable to quantify about 7-day changes and their uncertainties, CIs.

The third and fourth rows show changes in the phase, φ, of a 7-day cosine curve for analyses made on 0.5- and 1.0-year intervals, respectively, displaced for consecutive computations in increments of 28 days. For the first 12 years, the peaks occur mostly on or near Thursdays, irrespective of the interval length, more smoothly with the longer interval. The corresponding amplitudes remain comparable with earlier ones for the entire span, as shown in row 2. An advance in φ (downward trend at A) is also smoothed by using a 1.0- instead of a 0.5-year interval, but the following φ advance starting at B and continuing by scanning over

more than 1.5 full weekly cycles remains consistent during the last several years. The finding of this φ advance indicates an external circaseptan desynchronization of KS in a clinically healthy man, CH. An about (~)-weekly (circaseptan) cycle is synchronized in the first 12 years with the calendar week, while in the last 3 years, perhaps because he self-administered a more massive dose of androgen (as noted, the corresponding data are omitted from the analyses), a circaseptan τ of KS was slightly but statistically significantly shorter than a week, desynchronized from the societal calendar week, with which it had been previously synchronized for the preceding 12 years. For the last 3 years, the φs follow a diagonal advancing time course.

Do KS take a time course of their own at least in part? If so, is there an environmental counterpart as in the case of 24-hour rhythms? The alternation of light and darkness constitutes an environmental cycle to which circadian rhythms constitute an adaptation. In looking for a comparable physical environmental counterpart for the desynchronized week in us, we encountered a near-7-day cycle in geomagnetism (93), confirmed by others (94, 95). A cosinor spectrum reveals a dominant natural near-week of 6.74 days length in geomagnetism. Some years earlier Charles Greeley Abbot had "discovered a well-marked period … of 6.6456 days (later improved to 6.6485 days) and also the half of it in the weather of New York and Washington" (Abbot, 1963; see *Figure 25B*). Selectively assorted sets of about-weekly geo-, helio- and biospheric periods were then found in a clinically healthy man (176), *Figure 39A* (cf. *Figure 39B* for their aeolian behavior). It was tempting to postulate, on the basis of extensive experience with the week in us and around us that, for each biological cycle, there should be a corresponding environmental cycle, and vice versa. © Halberg.

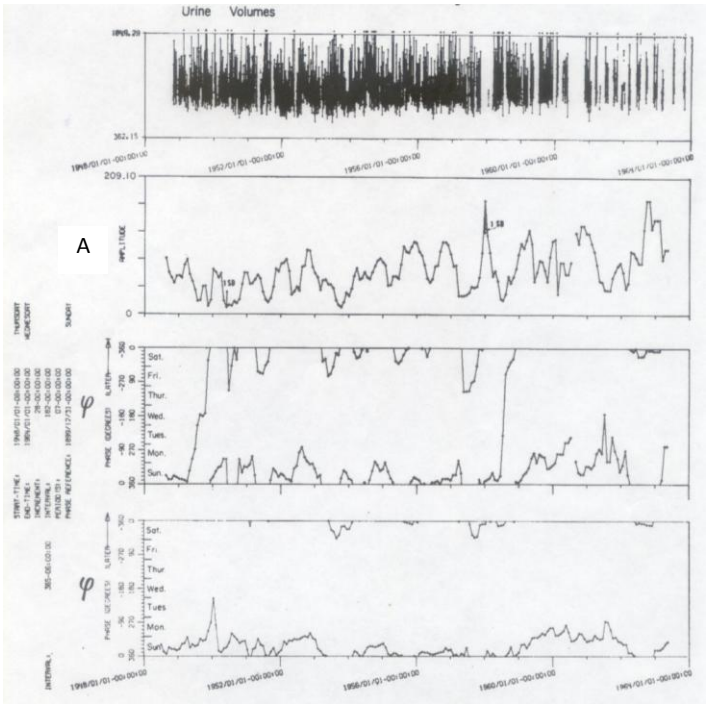


Figure 52E. A corresponding φ advance is not seen for urine volume, which observation renders desynchronization in KS even more remarkable as an indicator of a circaseptan internal desynchronization as well. © Halberg.

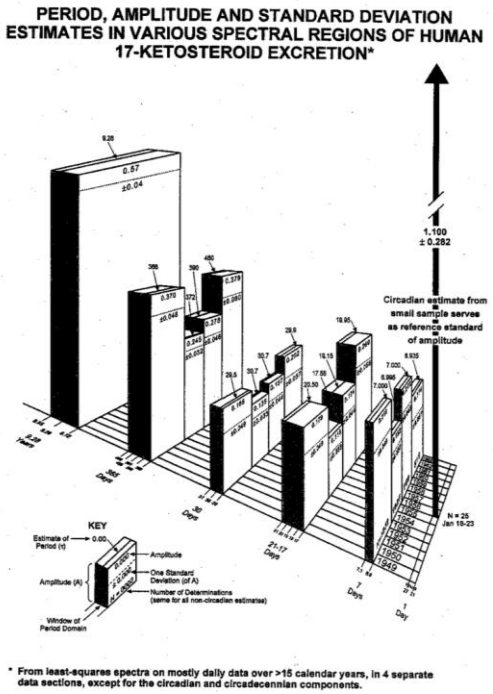


Figure 52F. It also seemed logical to ask whether the long biochemical 17-KS series actually also had a component of nearly 10 years, possibly associated with the sunspot cycle of Christian Pedersen Horrebow (1718-1776) (Thiele ThN. De Macularum Solis antiquioribus quibusdam observationibus Hafniae institutis. Astronomische Nachrichten 1859; 50: 259-261) and Samuel Heinrich Schwabe (1789-1876). An answer in the affirmative shows an about 10-year component found linearly in the spectrum with a period of 9.28 years which upon nonlinear analyses was longer with a CI covering 10 years (169). © Halberg.

Contradictory Correlations of Hormonal Metabolites with Age (I, II, IV - 5 of them) or with Solar Activity (V - 5 of them) Stem in part from a Common Years-Long Cycle (III, IV, VI)

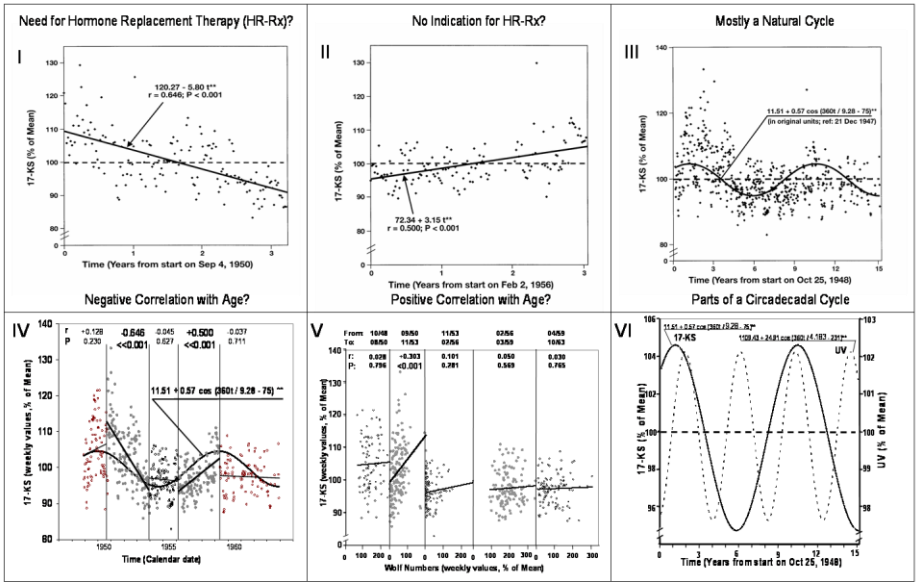


Figure 52G. In seeing just the steady decrease in KS (without knowing that it is part of an about

10-year cycle), CH, a medical professional, indeed considered the need for androgen substitution therapy (upper left graph). He may not have realized that a decreasing trend was a transient, followed by an increase (upper middle graph), the increase and decrease being but part of a readily seen cycle (upper right graph) that when related to age (lower left) or to sunspot numbers (lower middle) can lead, during different subspans, to contradictory, even opposite correlations (when examined only as a trend, in the absence of prior information). The circadecennian τ of 17-KS and the τ of urine volume differ (extreme bottom right). There are circadecennian, circaseptan and further transyearly differences between the τ of KS and the volume of urine in which it was determined and even differences in φ at the same τ, *Figure 52O*. © Halberg.

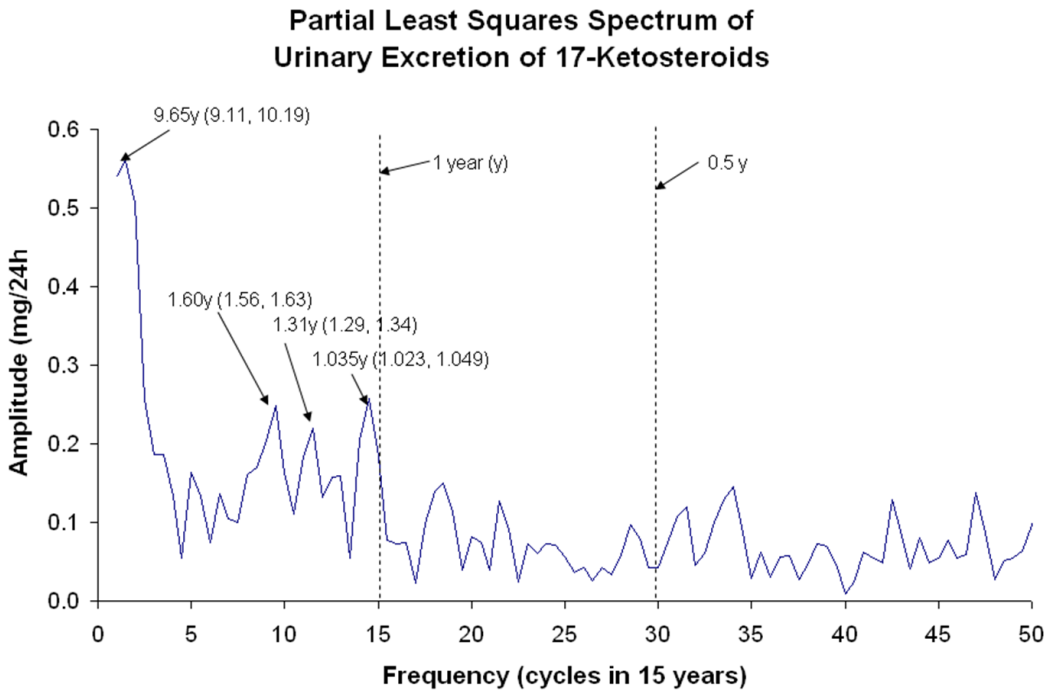


Figure 52H. On the data as a whole, a spectral window reveals (globally) novel periods (shorter and longer than a year) for KS of CH. © Halberg.

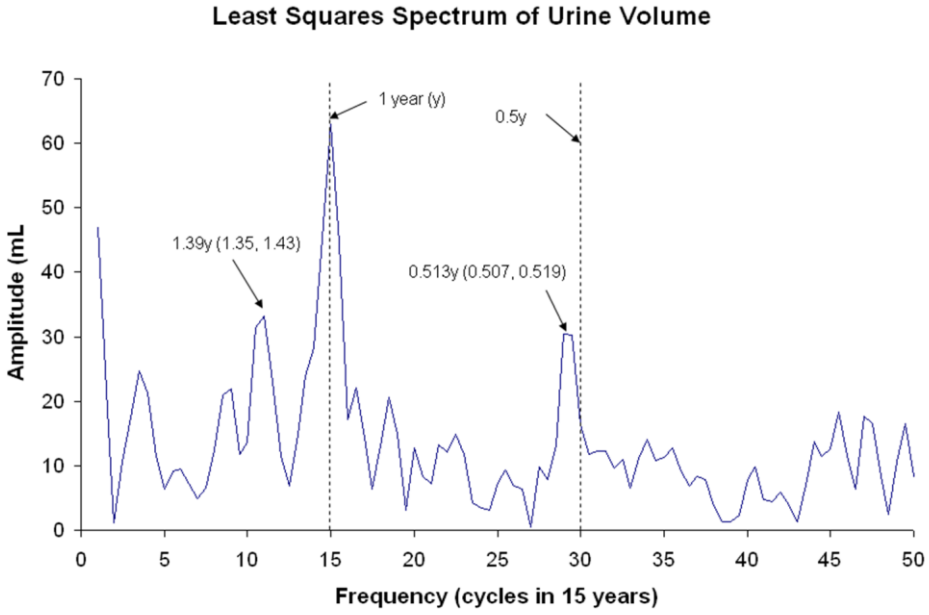
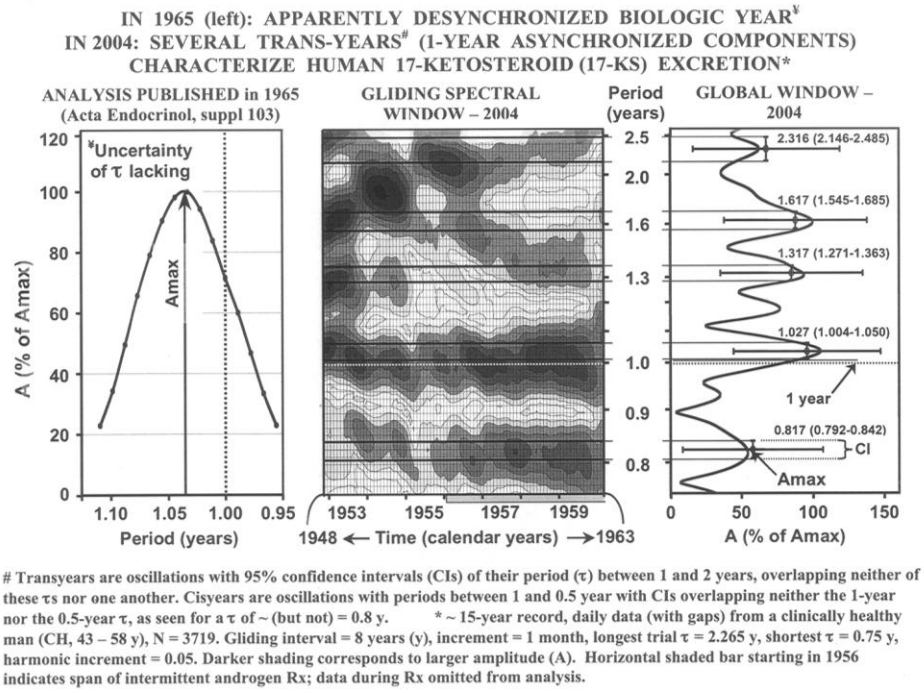


Figure 52I. On the data as a whole, a spectral window reveals (globally) novel periods for urine volume of CH. © Halberg.



Transyears are oscillations with 95% confidence intervals (CIs) of their period (τ) between 1 and 2 years, overlapping neither of these τs nor one another. Cisyears are oscillations with periods between 1 and 0.5 year with CIs overlapping neither the 1-year nor the 0.5-year τ, as seen for a τ of ~ (but not) = 0.8 y. * ~ 15-year record, daily data (with gaps) from a clinically healthy man (CH, 43 – 58 y), N = 3719. Gliding interval = 8 years (y), increment = 1 month, longest trial τ = 2.265 y, shortest τ = 0.75 y, harmonic increment = 0.05. Darker shading corresponds to larger amplitude (A). Horizontal shaded bar starting in 1956 indicates span of intermittent androgen Rx; data during Rx omitted from analysis.

Figure 52J. A glocal analysis, with a global window (right) and a gliding window for local study (middle) show a near-transyearly period of KS in CH that can globally (left) be separated from a yearly component by a 95% confidence interval (CI) not overlapping the precise 1-year length, unless the (conservative) CIs are still too liberal. Three far-transyearly periods are also seen glocally (middle and right). © Halberg.

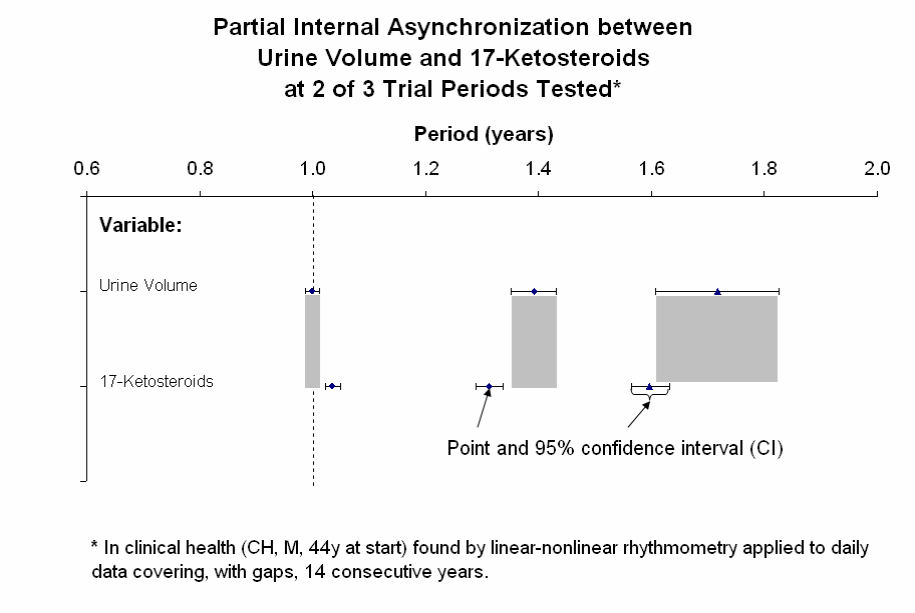


Figure 52K. Near-transannual (left) and far-transannual internal desynchronization of KS from urine volume in CH, suggested by non-overlapping 95% confidence intervals of the period estimates. © Halberg.

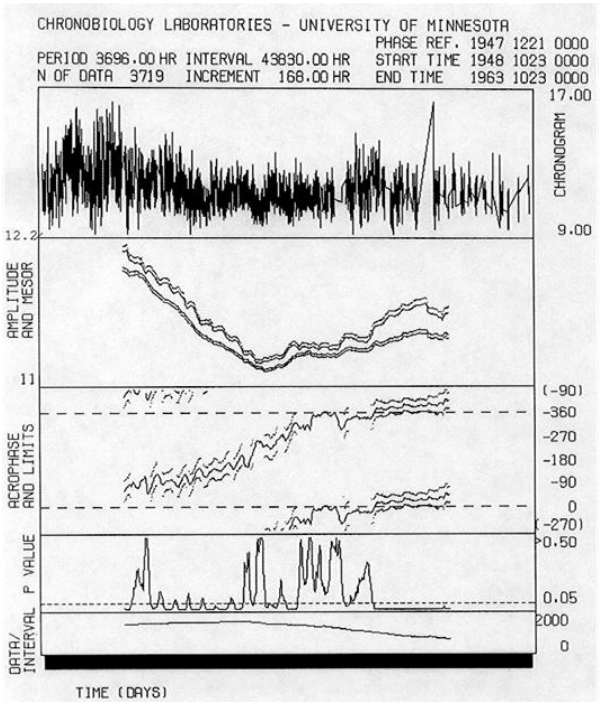


Figure 52L. The chronobiologic serial section shows the urinary KS data (top row) recorded over 15 years in CH, a clinically healthy male scientist 49 years of age at start of study. The MESOR, M, is the lower curve and the quinmensal's (cis-half-year's, 0.42-year's) amplitude, A,

is the distance between the two curves in the second row. Dots below the lower and above the upper curves indicate the standard errors of the estimates of M and A, respectively. Acrophases (third row) are shown with dots, corresponding to their CIs (95% confidence intervals) only when the P-values for the test of the "no 0.42 year" amplitude (shown in the fourth row) are below 0.05, the dashed horizontal line. The time course of cis-half-year acrophases mimics the time course of a 0.42-year component in the planetary geomagnetic index, Kp, *Figure 52M*. Globally, urine volume is congruent in period with the former two variables, but its phase behavior is congruent with neither; only transiently it seems to mimic the time course of the phase of the relative sunspot (Wolf) numbers which differs in its time course from those of KS and Kp (not shown). The two biospheric variables differ in terms of their environmental phase synchronization. © Halberg.

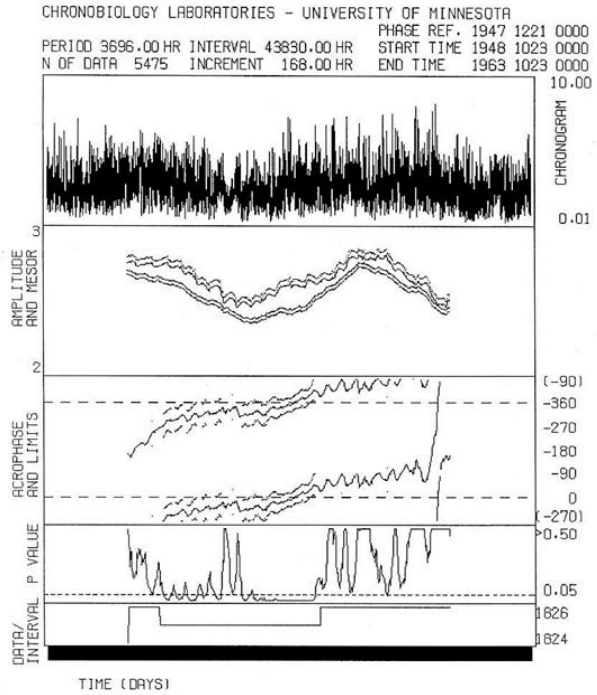


Figure 52M. A chronomic serial section of the planetary geomagnetic index Kp from October 23, 1948, to October 29, 1963, matching the KS record of CH, with the fit of a 0.42-year cosine curve shows a similar time course of quinmensal acrophases as that of CH's KS in *Figure 52L*. Note that statistical significance is lost toward the end of the record for Kp, but not for KS (*Figure 52L*). Note further at the beginning the lack of statistical significance in Kp, but not in KS. Note the quinmensal amplitudes (As, second row) that are quite large for KS at the end of the record, while the quinmensal (cis-half-year) is not statistically significant in Kp and its amplitude decreases with time. Time course of only intermittently congruent (possibly driving when present) environmental period resembles that of a biospheric period. Note, however, the persistence of a quinmensal period in the biosphere (when the previously congruent environmental period is not detected), suggesting a partial endogenicity in biospheric associations with the cosmos. These associations are preferably studied when all data series are equidistant and are the longest available, matching data series at a given time. Problems arise when at least one series is unequidistant because of artifacts that can simulate a periodicity when none exists and, vice versa, can obscure a real periodicity to the point that it is no longer detected. © Halberg.

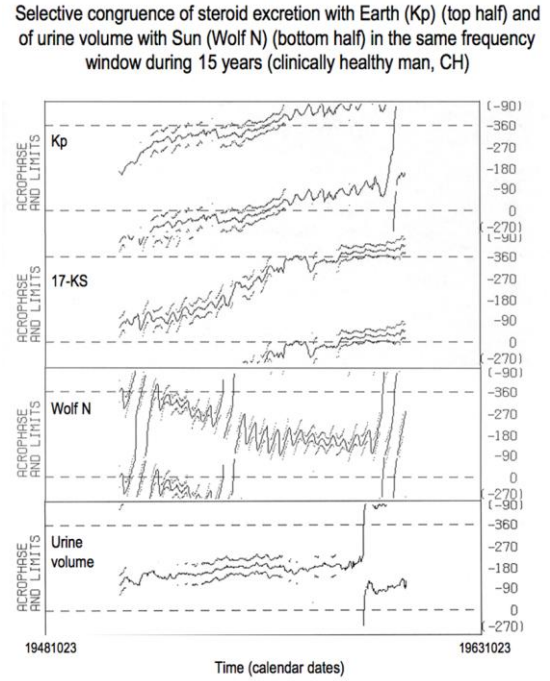


Figure 52N. Different drummers seem to lock-in the phase at a common quinmensal period tested of KS and urine volume in the same person? © Halberg.

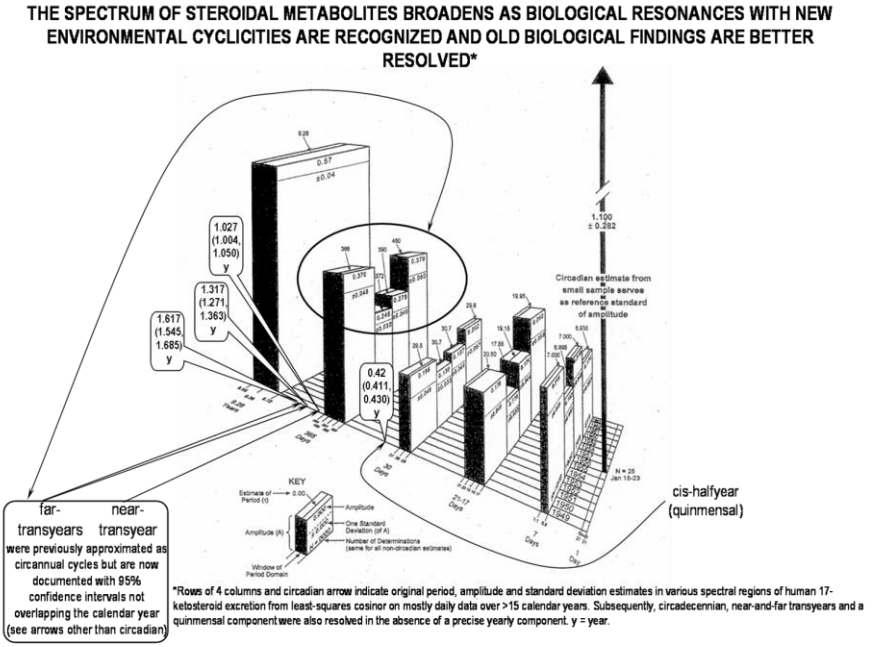
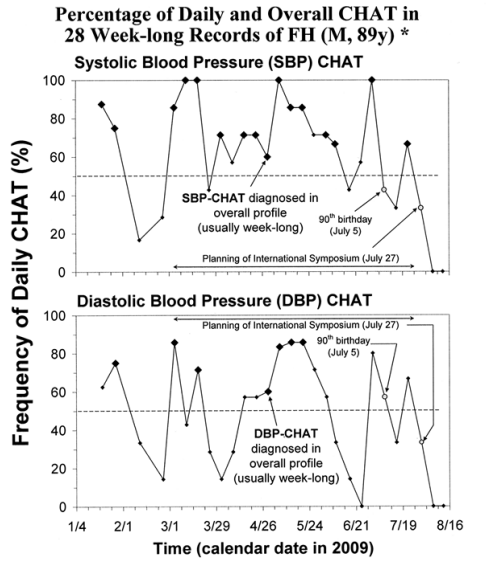
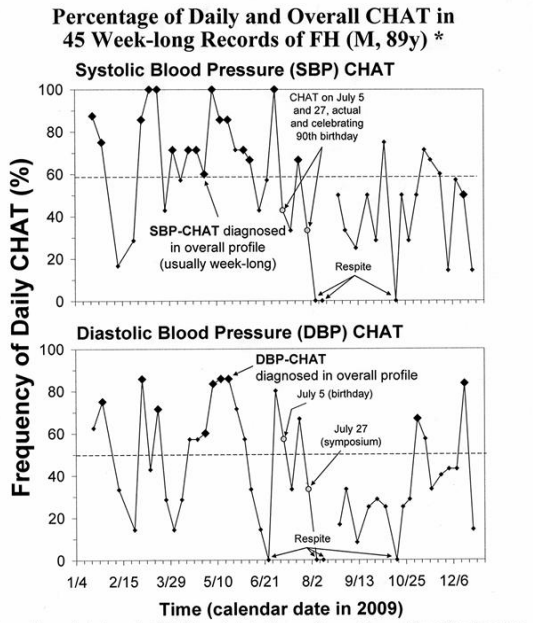


Figure 52O. Periodicities revised by 2012 (as compared to 1965 in *Figure 52B* and to 2001 in *Figure 52F*) in the breakdown products of steroidal hormones essential for survival and reproduction, the 17-ketosteroids; probably many more components will eventually be mapped as methods of analyses are refined and cross-validations become possible with novel physical co-periodisms or vice versa, or novel biospheric components prompt a search for environmental ones. © Halberg.



* Large diamonds indicate that CHAT was detected in overall record, irrespective of the percentage of the daily occurrence of CHAT (Circadian Hyper-Amplitude-Tension, "overswing"), a condition characterized by a 24-hour amplitude of blood pressure (in a 2-component model consisting of cosine curves with periods of 24 and 12 hours) exceeding the upper 95% prediction limit of clinically healthy peers matched by gender an age, associated with a large increase in cardiovascular disease risk. Whereas occasional daily CHAT is found in many usually week-long profiles, it is present overall in only a few records, day-to-day changes in MESOR and circadian acrophase contributing to a reduction in the 24-hour amplitude estimated from the entire records.

Figure 53A. CHAT during about 5 months of preparation for a symposium lost in the last 2 post-symposium records, each of 1-week duration. It would seem that after 14 days of normalcy, monitoring could be dispensed with. But consider revising this opinion in view of the following addition in *Figure 53B.* © Halberg.



* Large diamonds indicate that CHAT was detected in overall record, irrespective of the percentage of the daily occurrence of CHAT (Circadian Hyper-Amplitude-Tension, "overswing"), a condition characterized by a 24-hour amplitude of blood pressure (in a 2-component model consisting of cosine curves with periods of 24 and 12 hours) exceeding the upper 95% prediction limit of clinically healthy peers matched by gender an age, associated with a large increase in cardiovascular disease risk. Whereas occasional daily CHAT is found in many usually week-long profiles, it is present overall in only a few records, day-to-day changes in MESOR and circadian acrophase contributing to a reduction in the 24-hour amplitude estimated from the entire records.

Figure 53B. After the absence of CHAT in each of two consecutive weekly records, transient CHAT (small diamonds) recurs in both the systolic and diastolic blood pressure of FH with

weekly CHAT (bigger diamond) in one episode in systolic BP and two episodes in diastolic BP. There was no reason to lull oneself into a false sense of safety in *Figure 53A* based on the last 2 consecutive acceptable 7-day records therein. The full normality in the 2 weeks after a successful symposium was followed by transient (daily) CHAT and even occasional weekly CHAT. Take-home lesson: *Once a VVD is diagnosed, continued monitoring is advocated.* © Halberg.

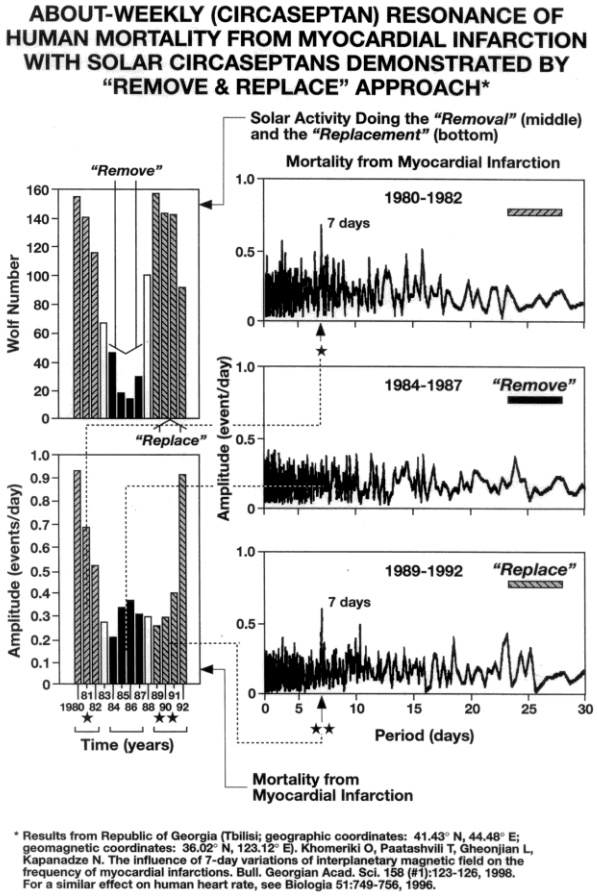


Figure 54. Mortality from cardiopathology in Tbilisi, Republic of Georgia (1980-1992) (177) is characterized by an anticipated weekly variation, a prominent circannual rhythm, and an about 10.5-year cycle similar to that observed for mortality from myocardial infarction in Minnesota (1968-1996) (178). Corroborating results on human heart rate (104), the circaseptan component is more prominent during spans of high solar activity than during solar quiet when solar circaseptans also tend to be more prominent (179). This about-weekly (circaseptan) resonance of human mortality from cardiopathology with sunspot circaseptans was demonstrated by a subtraction-addition procedure by Khomeriki et al. (177) corresponding to our "remove and replace" approach. © Halberg.

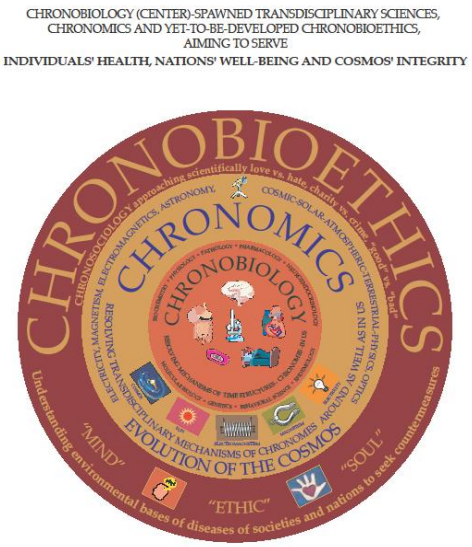


Figure 55. Chronobiology (center), starting in Minnesota with blood cell and mitotic counts (microscope), electroencephalograms, and endocrine, nucleic acid and other chemistry, spawned transdisciplinary tools, chronomics, aligning and investigating time series from us with environmental ones and yet-to-be-developed chronobioethics. These endeavors aim to serve the health of individuals and the well-being of society by the avoidance of personal and population disasters, such as massive strokes, crime and war, or earthquakes, and for avoiding personal and human-made or natural cataclysms and evading or at least understanding natural disasters. Chronoastrobiology is as yet missing in this diagram, has milestones in Figures 4 and 5, introducing remove-and-replace experiments, and Figure 44, documenting an association of human mood with interplanetary and earth magnetism. This may open a chapter in global health care including self-surveillance of populations to prevent or avoid personal and societal or natural environmental cataclysms, respectively. © Halberg.

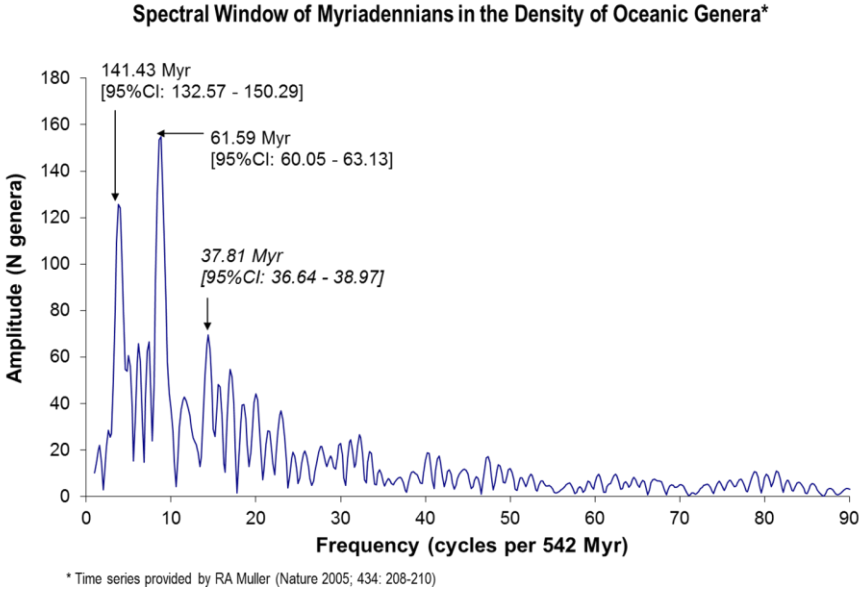


Figure 56A. A further step toward a tentative cross-validation of biospheric coperiodisms with cycles in (space) weather, a development that started vice versa from the natural biologic

nearweek slightly shorter than 7 days in 17-ketosteroid excretion, *Figure 24*, to a near-week of 6.74 days in geomagnetism, *Figure 25A* (cf. *Figure 25B*).

Data on fossil diversity during the Phanerozoic, the eon during which hard shells and skeletons left abundant fossils 0 to 542 million years (Myr) ago, formatted and previously analyzed by Rohde and Muller who reported about 62- and 140-Myr cycles (110) based on Raup and Sepkoski's compendium of the first and last stratigraphic appearances of 36,380 marine genera (Science 1982; 215: 1501-1503), were analyzed by linear-nonlinear rhythmometry (111). In addition to the two major spectral peaks reported by Rohde and Muller (110), the least squares spectrum of the residuals from a third-order polynomial trend reveals a third component with a period of about 38 Myr. Nonlinearly, a model consisting of the two major cycles and a third-order polynomial yields the 95% confidence intervals (CI) for the periods listed near the spectral peaks. When added to the model, the third component is also resolved with statistical significance, as shown in italics near the spectral peak. The addition of this component to the model results in only minor changes in the estimated periods, amplitudes (in thousands of genera) and their respective 95% CIs, estimated as 141.52 [132.14, 150.90] Myr with an amplitude of 143.5 [77.5, 209.5], 61.51 [59.98, 63.05] with an amplitude of 158.9 [133.2, 184.6], and 37.81 [36.64, 38.97] Myr with an amplitude of 75.8 [13.6, 138.0] (111). © Halberg.

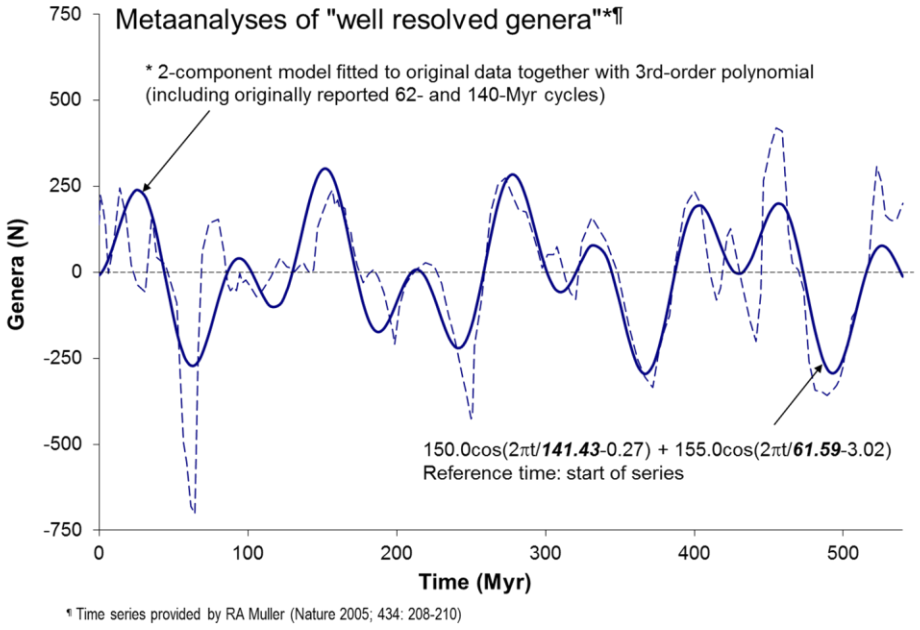


Figure 56B. Plot as a function of time of the well resolved genera (after removal of a third-order polynomial trend) together with the nonlinearly resolved model, considering only the two major spectral components reported by Rohde and Muller (110). © Halberg.

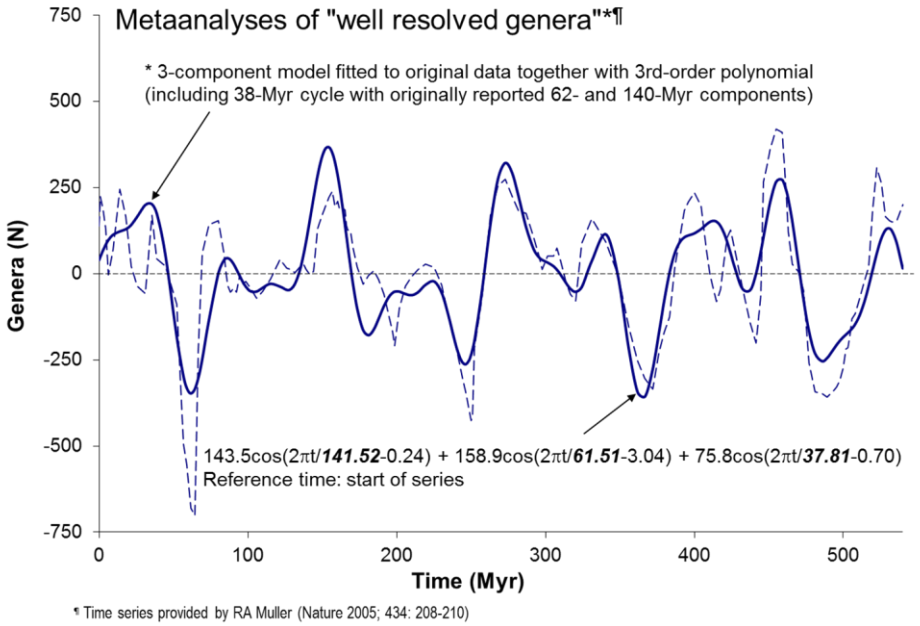


Figure 56C. Plot as a function of time of the well resolved genera (after removal of a third-order polynomial trend) together with the nonlinearly resolved model, considering all three spectral components detected by linear-nonlinear rhythmometry. © Halberg.

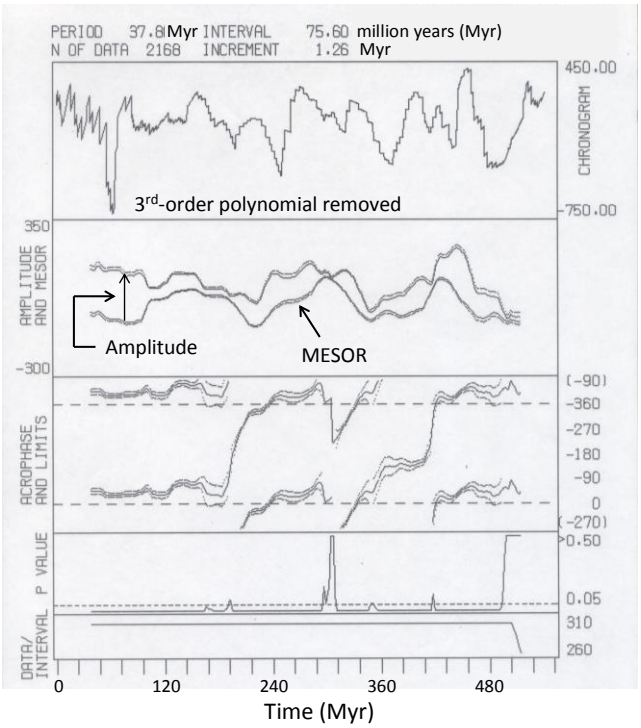


Figure 56D. Chronobiologic serial section of the "well-resolved genera" detrended by means of a third-order polynomial examines the stability of the about 38 Myr cycle characteristics, that may have an environmental coperiodism in the Hans Stille geologic 30 Myr cycle. The

detrended biospheric data on species diversity are shown in the top row. Instead of analyzing the time series as a whole, data are fitted with a 37.8 Myr cosine curve in a 75.6 Myr interval that is progressively displaced by a 1.26 Myr increment. The rhythm-adjusted average (MESOR) is the lower curve in the second row, and the 37.8 Myr amplitude is the distance between the two curves in the second row. Dots below the lower curve and above the upper curve are standard errors of the MESOR and myriadennian amplitude, respectively. The 37.8 Myr acrophases (phases of the maximum) are double plotted in the third row, where 0˚ corresponds to the beginning of the time series and 360˚ represent a full 37.8 Myr cycle. For the first ~150 Myr, the acrophase remains stable, then undergoes a rapid change around 180 Myr to resume about the same phase position until about 300 Myr when a longer lasting disturbance is associated with a shift of the acrophase by almost half a cycle (almost complete reversal). The acrophase returns to its original position after the 400 Myr mark. Changes in acrophase tend to coincide with times when the amplitude is smaller. Statistical significance for the 37.8 Myr fit is shown in the fourth row, indicating that the cycle is detected most of the time, except for short spans when the amplitude is reduced and the acrophase deviates from its original position. © Halberg.

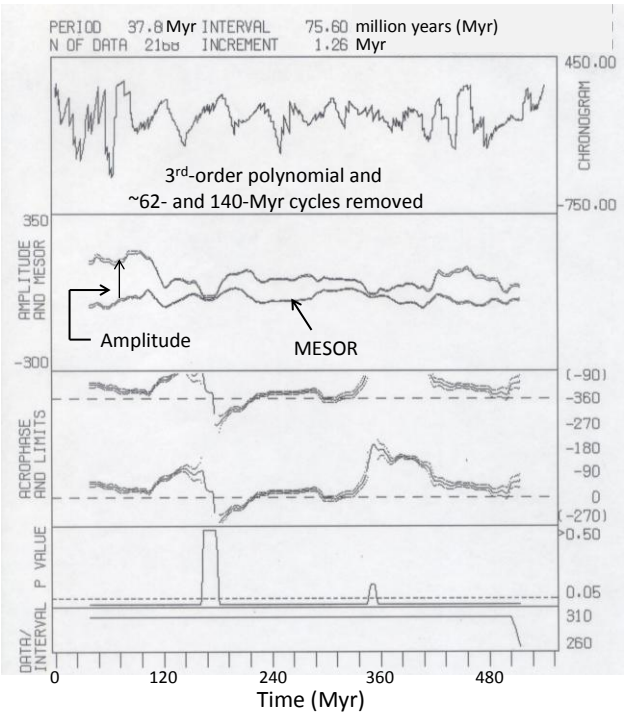


Figure 56E. The about 38 Myr cycle being less prominent than the about 62- and 140-Myr components, it is likely that the latter influence the estimation of the former in short intervals moved throughout the time series (in Figure 56D). For this reason, another chronobiologic serial section is obtained after removal not only of the third-order polynomial but also of the two largest cycles with periods of about 62 and 140 Myr, estimated nonlinearly and concomitantly. Residuals are shown in the top row. Whereas disturbances in the 37.8 Myr acrophases are still present, coinciding with spans when the amplitude is reduced, the stability and consistency of the acrophase is improved by comparison with results in *Figure 56D*. © Halberg.

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"ALL TIMES AND SEASONS OBEY YOUR LAWS[10]"

A brief overview of Professor Franz Halberg's life and work

Botond L. Buda

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Franz Halberg was born in Bistritz (Beszterce, Beszterce-Naszód County, Transylvania, Central-Eastern Europe) on July 5, 1919. His enthusiasm about poetry has been apparent from his early ages. However, his father, a renowned international lawyer who loved medicine, dissuaded him from becoming a poet which he originally wanted to be. (However, Professor Halberg still practices poetry on occasion in a contribution to a scientific academy or on birthdays of friends[11].) Thus, in 1936–1937 he started to study mathematics and physics. Although he never gave up his love for physics, it soon turned spontaneously into interest in a unified science. So he enrolled newly as a medical student and received his degree on the Royal Hungarian Ferenc József University in Kolozsvár (Kolozs County, Hungary, after the World War II Romania) in 1943.

The contemporary Hungarian government made all efforts in order to revitalize the Kolozsvár University after the Second Vienna Award (1940) and to re-integrate it into the high level international scientific life. Some of the newly appointed professors (Dr. Miskolczy Dezső, Dr. vitéz Berde Károly, Dr. Gyergyay Árpád, Dr. Lőrincz Ferenc, Dr. Horváth Béla, Dr. vitéz váradi Haynal Imre, Dr. vitéz kibédi Varga Lajos, Dr. Méhes Gyula, Dr. Haranghy László, Dr. vitéz Páll Gábor, Dr. Klimkó Dezső, Dr. Annau Ernő, Dr. vitéz Novák Ernő, Dr. Koleszár László, Dr. Vásárhelyi János, Dr. Mihálik Péter, Dr. Ludány György, Dr. Krompecher István, Dr. Móritz Dénes) were really magnificent physicians, famous scientists and brilliant tutors, while others, unfortunately, not as much.

Franz Halberg was, to all intents as purposes, not as lucky with his laboratory professor as my father with his beloved professor, the other internist of the Kolozsvár Medical School at that time, Dr. vitéz váradi Haynal Imre. As a medical student Halberg had a laboratory from Dr. vitéz kibédi Varga Lajos in the department of medicine of the university in Kolozsvár but achieved nothing[12]. So after the

[10] Preface of Sundays in Ordinary Time V

[11] Personal communication, 2012

[12] Personal communication, 2012

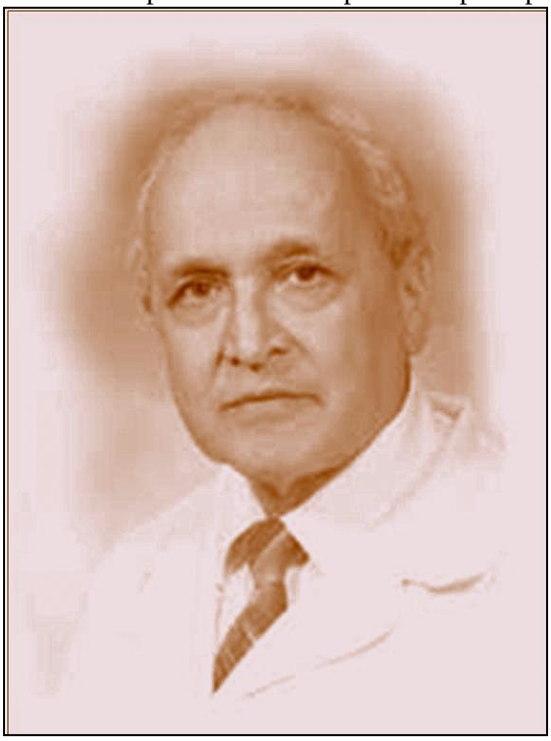
World War II he moved towards Austria hoping he could find a place with a more inspiring scientific climate and better opportunities than in the post-war Romania. He stopped in Tyrol (Austria), where initially he worked as a scientific assistant and later as a university assistant (1946–1948) in the Department of Anatomy of the Innsbruck University.

Photo: Franz Halberg in Budapest, Hungary, 1942

In contrast to some published biographies, it was *not* Innsbruck where Franz found his late first wife Erna whom he met only later in Minnesota. Innsbruck, the Tyrolean capital, interestingly, served as the scene of the encounter and dance with Erna's sister, Lotte[13]. Contact with a group of leading U. S. scientists teaching in post-war Europe resulted in an invitation to come to the United States where Halberg could find a significantly broader scope of research opportunities.

He left Europe and went to the U. S. in 1948 on a World Health Organization fellowship, where first he became a Research Fellow at Harvard Medical School and an Assistant in Medicine at the Peter Bent Brigham Hospital in Boston, Massachusetts.

In 1949 he moved to Minneapolis, where "water is blue like the sky". Here he joined the staff of the University of Minnesota Medical School. The inspiring scientific atmosphere of Minneapolis and perhaps the role model of both parents guided the Halberg daughters, Julia and Francine towards a medical and scientific career. Franz Halberg was the founder and is even at present the Co-Director of the Halberg Chronobiology Center in Minneapolis, where he has been, practically even after his retirement, continuously working, teaching, tutoring and researching for the past sixty years. There is no place and no need for detailing the numerous honorary doctorates, professorships, awards, medals or diplomas his long and productive scientific career acknowledged with. At the end of this laudation a brief scientific biographical sketch can be found, where Professor Halberg's major research experiences, honors, scientific functions, publications and contributions can be looked up by all who are interested.



There are, however, some pivotal items in Franz's life-work must to be exposed.

He was the one in the 20th Century who undisputedly placed time as a fourth dimension in life sciences, a new dimension, without which life on planet Earth could not exist. Thus, Professor Halberg is considered worldwide as the founder, father and doyen of chronobiology. More

[13] Personal communication, 2012

than half a century ago he also coined the term circadian which was referred to by "chronosceptics" as "Halberg's paranoia". He contributed chronobiology, the computer-aided science of the body's time structure, and framed the term chronomics as well. Three entities have been identified to constitute a broad time structure (the chronome): multifrequency rhythms, trends (as a function of age and also as a function of disease risk or response to treatment), and the as-yet unresolved variation (noise). More recently, the term chronobioethics has been coined by him as well, in the endeavor to quantify endeavors aiming at the so hard to define "good ".

The first moment, when even laymen could realize that dealing with chronobiology and circadian rhythms is not an inanity was at the time when Halberg and Gupta succeeded in doubling the 2-year survival of patients with oral cancer by timing their radiotherapy according to a circadian marker rhythm, tumor temperature.

Another scientific breakthrough with great practical healthcare impact: is based on around-the-clock blood pressure monitoring; Franz identified circadian hyperamplitude tension, now called "CHAT," an increased swing in the amplitude of blood pressure that develops before a rise in mean blood pressure readings. Surprisingly, CHAT was found to be a greater risk factor for ischemic stroke than family history, obesity, high cholesterol, being male, regular alcohol consumption, smoking and having an elevated mean blood pressure. Additionally, it was found that patients with diastolic CHAT (those whose diastolic blood pressure varies by more than that of their peers during a day) have a 8.2 greater risk of having a hard event, such as an ischemic stroke within six years than those whose circadian blood pressure amplitude is within a normal range. As it also turned out, taking blood pressure medication at an undesirable time can cause CHAT. Nonetheless, the importance of treatment timing is usually underestimated by family practitioners and cardiologists.

The results of studies led to the creation of the famous "Womb to Tomb" project more than 20 years ago, which involved monitoring the blood pressure of pregnant women and neonates. The initiative has since been renamed the BIOCOS (an acronym for *bio*sphere and *co*smos) project and broadened its scope. The purpose of the initiative is to monitor heart rate, blood pressure and other variables *for preventive reasons in maintaining good health* and also to *understand better the effects of the cosmos on our physiology and pathology*.

The mapping of multifrequency rhythms and of other components of the chronome may be the keys to maintain good health and to recognize elevated risk of certain diseases in time so that preventive measures could be carried out before the onset of actual disease. Franz is convinced that measuring and interpreting *chronobiologically*, for example, blood pressure series will sooner or later enable mankind to prevent stroke and also to evade other cataclysms.

Halberg realized that the more constant we try to make our proximal environment, the better we recognize virtually spontaneous variability that reflects the changes around us, near and far. This seemingly chaotic variability has its own laws which can only be discovered and described by analyzing huge series of data and figures. Professor Halberg, perhaps one of the last Renaissance men is, however, the man of the figures as well. "*Quod non est in actis, non est in vita*." What cannot be found in or supported by files (data, figures, etc.), does not exist at all. And, conversely: if we listen carefully enough to the periodic signals in us and around us near and far in the cosmos, we may find new associations, new solutions and broaden our horizon.

That could be perhaps the inducement for all the challenging endeavors of Franz during his long and prosperous scientific career.

Folia Anthropologica is proud of the privilege to publish the Professor Halberg's brand new paper summarizing the history of chronobiology and giving a deep insight in the senior author's stirring endeavors and life. Let us thank you on behalf of the University of West Hungary as well, Professor Halberg, thank you for your trust and invaluable cooperation, Franz!

S C I E N T I F I C B I O G R A P H I C A L S K E T C H

N A M E	P O S I T I O N T I T L E
HALBERG, FRANZ **Date of birth: 05th July 1919**	**Professor and Co-Director** **Halberg Chronobiology Center**

E D U C A T I O N

INSTITUTION AND LOCATION	DEGREE	YEAR CONFERRED	FIELD OF STUDY
University of Cluj, Romania		1936–37	Mathematics, Physics
Royal Hungarian Ferenc József University, Kolozsvár, Hungary (now Romania)	M.D.	1943	Medicine
Harvard Medical School, Boston, MA, USA	Fellow	1948–49	Medicine

R E S E A R C H A N D P R O F E S S I O N A L E X P E R I E N C E :

Past: Scientific assistant (Wissenschaftlicher Assistent) and later university assistant (Universitäts-Assistent), Department of Anatomy, University of Innsbruck, Austria (1946–1948)

Research Fellow, Harvard Medical School; Assistant in Medicine, Peter Bent Brigham Hospital, Boston, MA (1948–1949)

On the staff of the University of Minnesota Medical School since 1949: Fellow (1949); Instructor (1950); Research Associate and Assistant Professor in Physiology (1951–1954); Assistant Professor, then Associate Professor in Division of Cancer Biology (1954–1958); Elsa A. Pardee Professor of Cancer Biology and Experimental Pathology (1958–1962)

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CONTRIBUTION:

Chronobiology: the computer-aided science of the body's time structure (from *chronos* = time, *logos* = science and *bios* = life) (Introduced in Halberg F.: Chronobiology [Ann. Rev. Physiol. 31: 675-725, 1969], with a follow-up in Halberg F.: Quo vadis basic and clinical chronobiology: promise for health maintenance [Am. J. Anat. 168: 543-594, 1983]). ***Chronomics:*** the mapping of chronomes (time

structures), i.a., for chrono-functional genomics, accounting for quantifiable, partly predictable road maps consisting of a spectrum of rhythms with periods covering over 10 orders of magnitude, organizing chaos, and undergoing trends. ***Chronobioethics:*** mapping characteristics of spiritual (e.g., religious) motivation, crime and war, as well as physical and other environmental variables, pertinent to diseases of society and of those of individuals (Biomedicine and Pharmacotherapy 2001; 55 [Suppl 1]: 153-190; Neuroendocrinol Lett 2001; 22: 359-384; cf. also Introduction to Chronobiology. Medtronic Chronobiology Seminar #7, April 1994, 52 pp, http://www.msi.umn.edu/~halberg/).

PUBLICATIONS:

3452 (and 8 in press) as of May 4 2012; complete bibliography available at http://www.msi.umn.edu/~halberg/ and http://www.franz-halberg.wosco.org.

INTERVIEW:

"Why Timing is Everything" by Paul J. Rosch, MD, FACP, in May 2010 issue of Health and Stress: The Newsletter of the American Institute of Stress

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TIMING IN BALNEOLOGY – OUTLINES OF THE SÁRVÁR SPA STUDY

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Abstract

In 2009 Buda et al. planned and launched a balneo-somnological survey in the just reopened bath of Csorna, North-West Hungary, aiming to target two special subgroups of patients suffering for restless legs syndrome (RLS) and chronic insomnia, respectively. Their sparse previous results suggested that external treatment could perhaps be effective in RLS, while chronic sleeplessness could beneficially be influenced by Csorna mineral waters taken internally (BUDA 2009). Unfortunately, after just a few months' functioning Csorna's bath went into liquidation again, thus the investigations could not be continued.

In the present paper authors intend to outline their conceptionally new spa research shortly starting in Sárvár region, Western Hungary. Unlike in the Csorna study, in the new Sárvár investigations, greatly inspired by Halberg's endeavors and and Cornélissen's analytical implementation (HALBERG 2012, CORNÉLISSEN 2012), a much broader scope will be opened, linking traditional spa therapy not only with some neurological or psychiatric conditions and sleep disorders, respectively, but with monitoring blood pressure and heart rate as densely as possible, in association with timing baths as well.

Seasons have apparently been specified in antiquity for the use of certain baths in certain locations. The timing of baths along the 24-hour scale with new attention to assessing a full 7-day (circaseptan) cycle is the purpose of the special design of our spa study announced in the present paper.

Introductory hydrogeology

The so called geothermal gradient of the Carpathian basin (Central Europe) is extraordinarily high, reaching even a degree interval of 180°F/mile (BOLDIZSÁR 1964, 1973). That means, in other words, that in the Carpathian Basin one needs to dig down into a depth of 33 feet to reach a 1°F degree higher temperature zone, while in the utmost part of the world 60 feet depth is needed for 1°F degree temperature elevation (BORSZÉKI 1979). Due to this unusual heatedness of the lithosphere several natural traditional hot water karstic springs are situated at the edge of the mountain regions near the Hungarian capital Budapest (*Buda thermal line*), near the shallow water lake Balaton (Hévíz), or, for example, at Harkány, Eger and Miskolctapolca, respectively. (PAPP 1942, SCHMIDT 1962). Several smaller luke-warm spas (Tapolca, Abaliget, etc.) are also based on such springs ascending on the foothills of Mesozoic mountain

ranges. The first thermal wells have been drilled at the springs, than the thermal water production had moved towards the deeper basement rocks. The intensive research for oil and gas in Hungary revealed new information about the deeper high-entalpy geothermal reservoirs and resulted in several popular hot water resorts situated far from the mountains, such as e.g., in the North-Western part of Hungary, Bük (1957), Sárvár (1961), Csorna (1969).

Local spa history

The recreational use of spas and baths in the Carpathian Basin was widespread in the Roman Age already. The public baths of the legionary fortress, the Thermae Maiores, were discovered during the first excavations in Aquincum in 1778 when one of the bath's halls came to light. However, the beginnings of the curative bath culture can be dated to the Age of the Árpádian kings. In 1178 the established monastery as well as a hospital with a bath near the thermal springs of Felhévíz, Buda. Not far from here, by the springs of Alhévíz a leprosory bath was founded by St. Elizabeth of Hungary. The renaissance baths of King Matthias are well known from the 16th Century scripts of Prince Primate Oláh Miklós (OLÁH 2003). We have exhaustive information about the state of the Buda spas before the Ottoman subjection of Hungary from Georgius Wernher, constable of the Sáros and Eperjes castles (WERNHER 1549). The latter writing is a turning-point in the balneological literature, too, since analytical observations are published in it.

The first by and large modern medicinal water analysis was carried out by the ”physicus” of Buda town, Stocker Lőrinc (STOCKER 1721). However, despite their widespread empiric usage in the 18-19th Centuries, scientific studies about external or internal curative administration (TÖRÖK 1859) of healing waters gathered momentum only two hundred years later.

The first water wells were drilled at the beginning of the 19th Century in Hungary. Zsigmondi Vilmos was the first who, after thorough research, managed to drill a 392 feet deep a thermal water well on the Margit-sziget in 1867. The well brought 12.500 US Barrels water/day, containing sulfide, calcium and magnesium. At that time this was the deepest water well in Europe; even the emperor Franz Joseph inspected the construction in 1868. In the 20th Century, as the drilling technology gradually developed, the more quantity of mineral goods and fossil energy sources were needed, the greater part of the country was explored by deep drillings (*Figure 1.*).

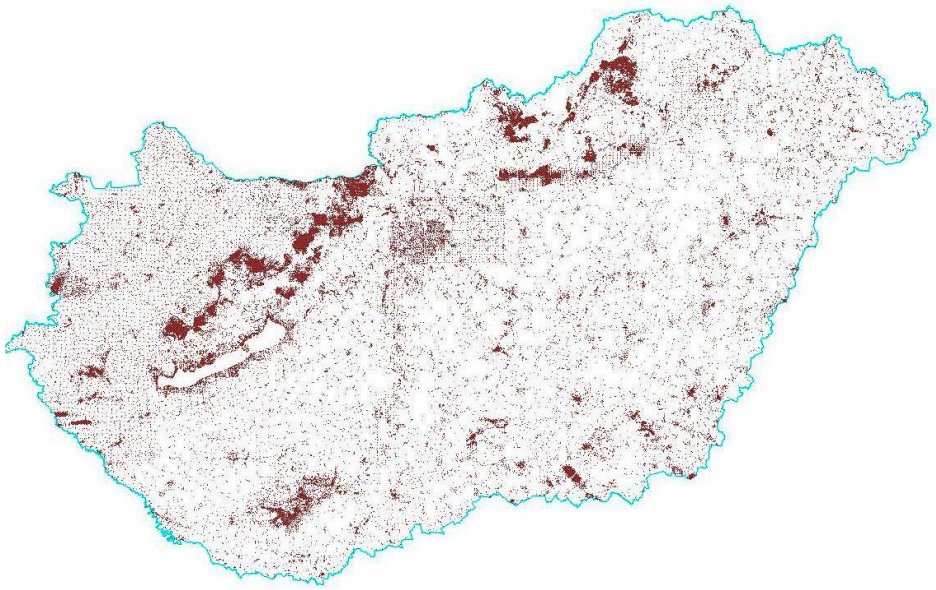

Figure 1. Geographical distribution of deep drillings in Hungary

During this exploration drillings, often just as a spin-off, high temperature thermal waters were found on several locations (CSEKE 1982, GÁL 1981, PERALTA 2004, SCHULHOF 1957, VITÉZ 1980), mostly and most abundantly from the Upper Pannonian sand and sandstone formations. On Hungary's 35.900 mi² territory more than 60 thousand deep drilled wells are officially registered at present – all of them either functioning or capable functioning.

Though it is less known (BENDER 2008) as in the case of locomotor disorders or gynecological complaints, heat and thermal water is used for a long while in neurological (FERBERT 2006, PÁKOZDY 1939, CSERMELY 2002, BALOGH 2005) and psychiatric disorders (SALAMON 2008), respectively, as well as in sleep medicine (VIDART 1977, SEKINE 2006). In 1969, at a drilling depth of 5.909 feet, 156°F hot waters with remarkably high soluble mineral content were found on the outskirts of the country town Csorna, Hungary (BODA 2001, BODA 2004, ZÁKONYI 1983). From the 1970's on, the outstanding healing property of the spa has been proved in chronic degenerative locomotor diseases and some disorders of the nervous system as well. However, balneotherapy ceased after few years.

Insomnia prevalence greatly depends on its definition and even more on the sample population. However, general consensus has developed from population-based studies that approximately 30% of a variety of adult samples drawn from different countries report one or more of the symptoms of insomnia: difficulty initiating sleep, difficulty maintaining sleep, waking up too early, and in some cases, nonrestorative or poor quality of sleep (ROTH 2007). Thus, taking into consideration the high prevalence of insomnia, in 2009 Buda et al. started a new study in the just reopened Csorna bath, aiming to target two special subgroups of patients suffering for restless legs syndrome (RLS) and chronic insomnia, respectively. Their previous results suggested that external treatment could be more effective in RLS, while chronic sleeplessness could beneficially be influenced by Csorna mineral waters taken internally (BUDA 2009). Unfortunately, after half a year's functioning Csorna's bath went into liquidation again, thus the investigations could not be continued.

The Sárvár Spa Study – location

Sárvár is a small town with a long history Western Hungary, situated on both banks of the river Rába, which is practically the geographic axis of Vas County, at the mouth of the brook Gyöngyös. The area has been inhabited since the late Stone Age. Before the Romans a Celtic tribe, the Boius, owned the ancient river crossing. Later Roman military camps were set up on both sides of the river. On the East of the river, there was a civic settlement established with the name of Bassiana.

Sárvár has been continuously inhabited in the post Roman times as well. The Hungarians built earth entrenchments against the attacking German forces around the X. century. The king owned the castle until the 1280ies. Charles I. Robert gave the inhabitants of Sársziget (today the inner part of the town) letters of patent. Nádasdy Tamás married Kanizsai Orsolya in 1535, which meant that the castle now belonged to the Nádasdy family. He established a true cultural centre in the crumbling, war-struck country: in 1534 he founded a school, in 1537 a printery, in charge of which he put Sylvester János, the teacher of the school. Sylvester translated the New Testament and printed it in 1541. Thus the first printed book appeared in Hungary. Nádasdy preferred having important scientists, doctors, humanist and artist around him. Tinódi Lantos Sebestyén, the famous lyre-player, died in 1556 and he buried in Sárvár.

People in search of oil found half a century ago something far more valuable than gold in the bowels of the earth: thermal water. At drilling depths of 3.275 feet in 1961 and 3.935 feet in 1973, respectively, 111°F luke-warm waters with characteristic mineral content were found. Thermal tourism is of key importance in the development since that time and for the future especially.

The Sárvár Spa Study – planned design

Seasons have apparently been specified in antiquity for the use of certain baths in certain locations. The timing of baths along the 24-hour scale with new attention to assessing a full 7-day (circaseptan) cycle is the purpose of the following design:

During 5 weeks interested volunteers would follow a design with a Latin square, such that one proband in sets of 6 subjects, picked by throwing dice, starts, e.g., at a specific span on awakening (and after one week takes a bath 4, then 8, then 12, and then 16-hours after awakening). Four others in a set of 6 subjects take a bath starting a one of the remaining times after awakening and complete the sequence, while a sixth subject doesn't bathe, but is monitored. The start time would be picked at random for each subject until he completes the sequence. During the entire 5 weeks, the 5 subjects and the control subject, except for the time when they actually bathe, will do automatic blood pressure and heart rate monitoring. This is recommended at half-hour intervals.

The data will be interpreted chronobiologically by both a parametric and a nonparametric design, in keeping with an international consensus (HALBERG 2008a, HALBERG 2008b). The scope of the analyses in addition to a sphygmogram will include a chronobiologic serial section, so that any changes in the parameter examined separately, namely period, amplitude, phase and waveform are extended during weeks involving bathing at a different time. Particular attention will be paid to the presence or absence of vascular variability anomalies such as alterations of MESOR (MESOR is an acronym for Midline-Estimating Statistic Of Rhythm; a rhythm-adjusted mean, usually better than the arithmetic mean; in unequidistant data, it is more accurate, and in equidistant data it is more precise), the amplitude, phase and waveform at each period of interest. Such a design has proved its value by showing differences in MESOR as a function of exercise at different hours after awakening. The arrangement of starting different patients at different times of awakening serves to explore any novelty effects.

Additionally, the Hungarian version of the reduced Horne-Östberg Morningness-Eveningness Questionnaire (URBÁN 2011), the Pittsburgh Insomnia Scale (MOUL 2002) and the Positive and Negative Affect Schedule (PANAS) (CRAWFORD 2004) is planned to be used. We intend to publish the first results of our analyses as sufficient data are getting gathered.

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THE KÖRMEND GROWTH STUDY — 1958–2008

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Abstract: Körmend is a small town in Western Hungary, Europe. The Körmend Growth Study was initialized in 1958 by Dr. Ottó Eiben. The measurements repeated in regular 10-year intervals revealed the first firmly reliable data in Central Europe to demonstrate the existence of secular trends in growth and maturation of children. This repetitive highly representative cross-sectional growth study proved to be a suitable tool for studying different aspects of secular trends as well as intergenerational differences. In this paper the authors present an overview of the five decades of the Körmend Growth Study. Over this half century the primarily rural settlement became a fairly industrialized town. Its population increased and its infrastructure improved remarkably. The growth characteristics of children also changed during this period. The physique of Körmend children became more linear but a bit fatter. The age at menarche also changed.
Keywords: Growth and maturation, Körmend Growth Study, Hungary

Introduction

Growth and maturation of children is a dynamic and complex biological process, influenced both by genetic and environmental factors. Children's growth pattern can change from time to time, there-fore, it is necessary to investigate the state of children's somatic development repeatedly. According to a widely accepted and scientifically proven theory, children's growth and maturation status is a fine indicator of the nutritional and health conditions of the general population. In other words, information about growth and development of children and youth mirrors the biological status and/or welfare of a population (TANNER 1978, 1994, EIBEN 1998).

The „Körmend Growth Study" (KGS), a chain of repeated cross-sectional growth studies performed on children in the town of Körmend (Hungary) was one of the first realizations of this principle. Anthropological investigations have been performed in Körmend in every 10 years since 1958 in a systematic way.

Secular trend is one of the most challenging human biological discoveries of the 20-21 Century. It is a world phenomenon, defined as a series of long-term systematic changes in a wide variety of human biological traits, in successive generations, living in the same territory. Secular trend has already been investigated at different population levels such as in newborn babies, in growing children, in young adults or in the whole population (EIBEN 1988, 1994). The KGS, as a chain of regularly repeated cross-sectional growth studies, is a suitable tool for studying not only several aspects of secular trend but distinct differences between successive generations as well (EIBEN 2002).

Materials and methods

The KGS was started in 1958 by professor Eiben. Dr. Ottó Eiben (1931–2004) was professor and chair at the Department of Anthropology at Eötvös Loránd University, Budapest, Hungary. The principal field of his scientific research activity included growth and maturation of children and the secular trend. He

repeated his investigations (K-58, K-68, K-78, K-88) decennially. In 1998 the study (K-98) was performed by Eiben and Tóth, while after Eiben's death the KGS has been carried on and K-008 (2008) was performed by Tóth (EIBEN and TÓTH 2000, TÓTH et al. 2009).

The aim of the study was to involve all healthy 3–18 year-old boys and girls living in the town, i.e. all preschoolers and school children. The representation has usually been well over 95%, except in case of K-98 (76%), and in case of K-008 (72%). Exercising their personality rights, several parents refused assisting the investigation in 1998 and in 2008. The last cross-sectional study (2008) has been carried out on 1563 children (757 girls and 806 boys) (*Table 1*). Decimal age of the subjects was calculated.

Table 1: Samples of the Körmend Growth Study (KGS)

Year of investigation	Study	Number of inhabitants in Körmend	Number of children investigated
1958	K-58	7500	1656
1968	K-68	10000	1736
1978	K-78	12000	2420
1988	K-88	12400	2867
1998	K-98	12200	2029
2008	K-008	12100	1563

The anthropometric program of the KGS was very extensive. 15 body measurements and 10 head and face measurements were taken in 1958 (K-58). In K-68 21 body measurements were taken, and during K-78, K-88, K-98 and K-008, on the basis of the same principle, 23 body measurements formed the anthropometric program.

Methods and techniques of the investigations were in accordance with internationally accepted standards described by MARTIN and SALLER (1957). The recommendations of the International Biological Programme, Human Adaptability section, were also taken into consideration (TANNER et al. 1969). Age at menarche was collected from girls, using the „status quo" method.

Eiben has published several papers about the KGS. He has summarized the results of the first three-four investigations in a small monograph (EIBEN 1988) containing a complete list of papers published about the KGS till then. Fifteen years later he has published another monograph about the ongoing KGS (EIBEN 2003). In this monograph he described all economic and social changes which influenced Körmend children's mode of life and somatic development. He pointed out that the population's relative genetic balance had somewhat altered, especially as an effect of the accelerated migration from the last decade of the 20th Century on.

Results and Discussion

Height: Average height increased almost monotonously in all age-groups and in both sexes during the study period. A positive secular trend was observed, however, height differences between consecutive investigations got smaller in the last decades.

The large mean height increase between K-58 and K-008 in several special age-groups is an especially fascinating of the past 50 years. In case of the 7 year-old boys (this is age of the first grade primary school classes) the mean height of 116.6 cm in K-58 increased to 128.9 cm in K-008. In girls, the same height measures were 117.5 and 124.3 cm, respectively. In the case of the 13 year-old pubescent boys, difference between K-58 and K-008 was almost 10 cm (149.6 and 159.3 cm, respectively). In the case of the same aged girls, the K-58 mean was 150.3 cm, whereas in K-008 it was found to be 159.3 cm. The 18 year-old boys, the so-called "young adults" were 168.8 cm tall in K-58, and 175.9 cm in K-008. Their female counterparts in K-58 had a mean stature of 161.5 cm, recently (K-008) 162.1 cm. It is worth mentioning that the average height values in the 18 year-old age group of K-008 were more or less equal with the estimated average stature of adult Hungarian men and women.

Weight: In the case of body mass, our findings were similar to the observations concerning the height data, i.e. average weight increased monotonously in all age groups and in both sexes. These changes were parallel with the changes in stature.

It is worth highlighting some important changes in weight in several special age groups. In 7 year-old boys, K-58 mean was 19.6 kg, in K-008 it was 23.1 kg. In girls, the correspondent means were 20.7 and 24.2 kg, respectively. The 13 year-old boys in K-58 weighted 38.0 kg, in K-008 this value was 49.5 kg. The girls' correspondent data were 39.1 and 47.4 kg, respectively. In the 18 year-old groups, there were no large differences between the K-58 and K-008 weight data. Mean values in boys were 61.2 and 70.6 kg, in girls 52.4 and 59.2, respectively.

Both in height and weight, a positive secular trend was observed.

BMI: Comparing distinct ten-year intervals from 1958 to 2008, a decreasing tendency of BMI can be observed in boys until the age of 8. However, beginning from the age of 9, these values begin to increase rapidly. This increasing process tends to get more dynamical from the age of 13, which corresponds the greater fat deposition in the hip and abdominal region at that age, especially in the epoch of K-008. That should draw our attention to the likelihood of later adulthood abdominal type obesity as a risk factor. The same tendency can be observed, somewhat attenuated, in girls. In girls, the subcutaneous fat volume did not increase that rate either, as it is characteristic in boys (SUSKOVICS and TÓTH 2011). Comparing the statistical parameters of body mass index of boys and girls, respectively, calculated in 2008 (K-008), stagnancy under the value of 15 kg/m^2 (or incidentally slightly exceeding it) can be stated in both genders until the age of 8. From the age of 9 on, increasing can be observed in both genders, however, there is no significant difference in the body mass index of boys and girls. From the age of 16, the increasing rate of the body mass index of girls slightly lags behind of that of boys.

The growth pattern of children: We have shown that the above mentioned changes in the growth pattern of children occurred at different time periods for girls and for boys; for girls it took place in the 1990s (K-98), whereas for boys it happened ten years later (K-008). These new findings correspond the results of earlier investigations, representing a significant step towards the understanding of gender differences in children development (TÓTH et al. 2012).

The physique of Körmend boys and girls became more linear but a little bit fatter during the study period. Recording of the values of biceps, triceps, subscapular, suprailiac, abdominal and calf skinfolds and the bicondylar parameters became part of the anthropometric schedule from 1968 on. Distinctive skinfold values were observed at different phases of the children's growth. Differences in early childhood skinfold measures – especially in the truncal region – increased with age and developed as a highly characteristic indicator of gender dimorphism by the prepubertal/pubertal age. The observed increase in truncal skinfold values, however, indicated an unfavorable tendency. Secular changes in skinfold measure were, in certain extent, due to the alterations of nutritional conditions and physical activity. Bone maturity values reflected the accelerative changes but not the secular trend. The lack of physical activity and the nutritional lapses were the major causes of this phenomenon (SUSKOVICS and TÓTH 2011).

The somatotypes of the boys: In 1968, besides the low values of the endomorphic component (an indicator of body fat), the main characteristics of the boys were the linearity and the dominance and balance of the components associated with bone-muscle development. 40 years later ectomorphy and endomorphy values apparently changed place. The dominant component was endomorphy, which is characteristically associated with high body fat content and the digestive system. There were no significant changes observed in the mesomorphic component. In contrast, the linearity component was significantly lower than the other two components. The observed changes could be explained based on a possible lifestyle change. A change in dietary pattern and physical inactivity could result in a significant increase of the abdominal skinfold and suprailiac skinfold measures (SUSKOVICS and TÓTH 2011), which caused a change in physique and the dominance of the endomorphic component (TÓTH et al. in press).

Age at menarche (*Figure 1*) has also changed over the previous decades (SUSKOVICS and TÓTH 2009, TÓTH et al. 2012). The age at menarche at the first study (K-58) was M=13.53 years. This was the highest age value revealed from any studies carried out at that time. Therefore, understandably, the value is higher than that of result of the national-wide sample in 1959-61 (Bottyán et al. 1963). The age at menarche in Körmend had been decreasing during the first period of the study's half century. By 1998 the age at menarche in Hungary reached the ever lowest value (M=12.75 years) (EIBEN 2001). This was followed by stagnation, then by a reversal of the trend.

The observed changes in children's growth and maturation patterns might reflect important changes in socio-economic conditions in the town. Moreover, the population of Körmend had undergone certain changes affecting its relative genetic balance because of the migrations observed in 1970-1980 (EIBEN 2001). A positive/negative secular trend seemed to be manifested both in Körmend girls and boys. The anthropometric data of the KGS documented many human biological effects of irreproducible social events and/or changes exactly and in a very quick and sensitive way (EIBEN and TÓTH 2005).

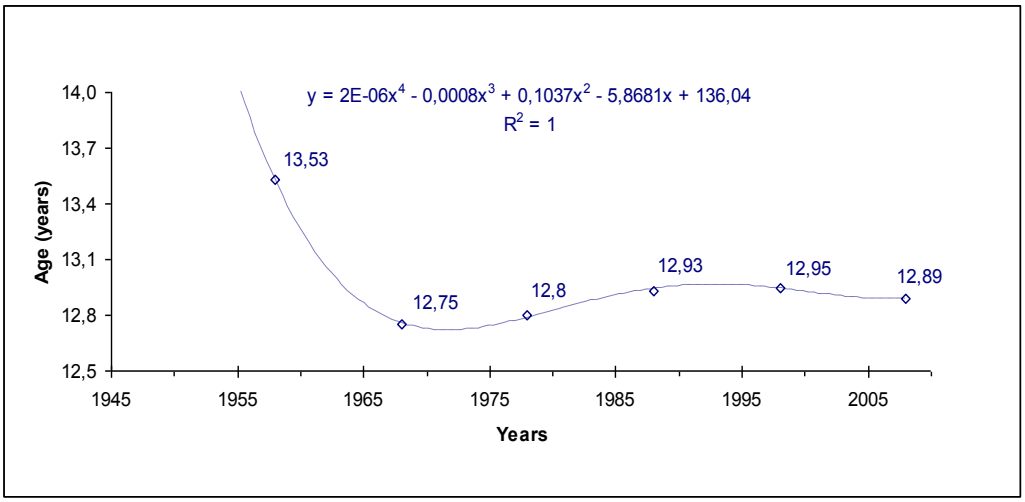

Fig. 1: Regression equations and trend lines for age at menarche in Körmend

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