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TIME STRUCTURES (CHRONOMES) IN US AND AROUND US

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In this the book the problems of chronobiology, chronocardiology, and chronoastrobiology in light of modern representations about mechanisms regulation of biological rhythms are shined.

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CONTENTS

INTRODUCTION

Structures in time are called chronomes; their mapping in us and around us is called chronomics. The scientific study of chronomes is chronobiology. And the scientific study of all aspects of biology related to the cosmos has been called astrobiology. Hence we may dub the new study of time structures in biology with regard to influences from cosmo- helio-and geomagnetic rhythms chronoastrobiology.

It has, of course, been understood for centuries that the movements of the earth in relation to the sun produce seasonal and daily cycles in light energy and that these have had profound effects on the evolution of life. It is now emerging that rhythmic events generated from within the sun itself, as a large turbulent magnet in its own right, can have direct effects upon life on earth.

Moreover, comparative studies of diverse species indicate that there have also been ancient evolutionary effects shaping the endogenous chronomic physiological characteristics of life. Thus the rhythms of the sun can affect us not only directly, but also indirectly through the chronomic patterns that solar magnetic rhythms have created within our physiology in the remote past.

For example, we can document the direct exogenous effects of given specific solar wind events upon human blood pressure and heart rate. We also have evidence of endogenous internal rhythms in blood pressure and heart rate that are close to but not identical to the period length of rhythms in the solar wind. These were installed genetically by natural selection at some time in the distant geological past.

This interpretive model of the data makes the prediction that the internal and external influences on heart rate and blood pressure can reinforce or cancel each other out at different times. A study of extensive clinical and physiological data shows that the interpretive model is robust and that internal and external effects are indeed augmentative at a statistically significant level.

The development of high technology instruments and computer power, already used to visualize the human heart and brain, is furthermore making it obvious that there is a statistically predictable time structure to the fluctuations in the sun's thermonuclear turbulence and thus to its magnetic interactions with the earth's own magnetic field and hence a time structure to the magnetic fields in organisms.

Likewise in humans, and in at least those other species that have been studied, computer power has enabled us to discover statistically defined endogenous physiological rhythms and further direct effects that are associated with these invisible geo- and heliomagnetic cycles.

Thus, what once might have been dismissed as noise in both magnetic and physiological data does in fact have structure. And we may be at the threshold of understanding the biological and medical meaning and consequences of these patterns and biological-astronomical linkages as well.

The evidence already mentioned that fluctuations in solar magnetism can influence gross clinical phenomena such as rates of strokes and heart attacks, and related cardiovascular variables such as blood pressure and heart rate, should illustrate the point that the door is open to broad studies of clinical implications.

The medical value of better understanding magnetic fluctuations as sources of variability in human physiology falls into several categories:

- The design of improved analytical and experimental controls in medical research. Epidemiological analyses require that the multiple sources causing variability in physiological functions and clinical phenomena be identified and understood as thoroughly as possible, in order to estimate systematic alterations of any one variable.
- Preventive medicine and the individual patients'care. There are no flat ‘baselines’, only reference chronomes. Magnetic fluctuations can be shown statistically to exacerbate health problems in some cases. The next step should be to determine whether vulnerable individuals can be identified by individual monitoring. Such vulnerable patients may then discover that they have the option to avoid circumstances associated with anxiety during solar storms, and/or pay special attention to their medication or other treatments. Prehabilitation by self-help can hope-

fully complement and eventually replace much costly rehabilitation.

- Basic understanding of human physiological mechanisms. The chronomic organization of physiology implies a much more subtle dynamic integration of functions than is generally appreciated.

All three categories of medical value in turn pertain to the challenges for space science of exploring and colonizing the solar system. The earth's native magnetic field acts like an enormous umbrella that offers considerable protection on the surface from harsh solar winds of charged particles and magnetic fluxes. The umbrella becomes weaker with distance from the earth and will offer little protection for humans, other animals, and plants in colonies on the surface of the moon or beyond.

Thus it is important before more distant colonization is planned or implemented to better understand those magnetism-related biological– solar interactions that now can be studied conveniently on earth.

Thorough lifelong maps of chronomes should be generated and made available to the scientific world. Individual workers should not have to rediscover cycles and rhythms, which can be a confusing source of variation when ignored. By contrast, once mapped, the endpoints of a spectral element in chronomes can serve everybody, for instance for the detection of an elevation of vascular disease risk.

Chronomic cartography from birth to death is a task for governments to implement, thereby serving the interests of transdisciplinary science and the general public alike. Governments have supported the systematic gathering of physical data for nearly two centuries on earth in order to serve exploration, trade, and battle on land and on the seas, and indeed agriculture. These government functions have been augmented enormously with satellite technology in more recent decades.

The biological comparison with regard to government support and chronomic needs would be the mapping of the human genome. The complete sequences of DNA might have eventually become available due simply to countless individual laboratories publishing piecemeal results in scattered journals. But there would have been enormous redundancy and confusion in assembling and piecing the information together. The waste of time and money involved in the redundancy and confusion would have been considerable. A coordinated effort to systematically gather the information and develop a system for cataloguing it was considerably more rational.

The exchanges that have taken place over four years of scientific meetings on this topic have confirmed the great scientific promise and potential practical value of chronomic lines of research, and also the need for larger and organized, sooner rather than later, life-span-covering physiologic monitoring initiatives.

Chronoastrobiology: are we at the threshold of a new science? Is there a critical mass for scientific research? A simple photograph of the planet earth from outer space was one of the greatest contributions of space exploration. It drove home in a glance that human survival depends upon the wobbly dynamics in a thin and fragile skin of water and gas that covers a small globe in a mostly cold and vast universe. This image raised the stakes in understanding our place in that universe, in finding out where we came from and in choosing a path for survival.

Since that landmark photograph was taken, new astronomical and biomedical information and growing computer power have been revealing that organic life, including human life, is and has been connected to invisible (non-photic) forces in that vast universe in some surprising ways.

Every cell in our body is bathed in an external and internal environment of fluctuating magnetism. It is becoming clear that the fluctuations are primarily caused by an intimate and systematic interplay between forces within the bowels of the earth – which the great physician and father of magnetism William Gilbert called a ‘small magnet’ – and the thermonuclear turbulence within the sun, an enormously larger magnet than the earth, acting upon organisms, which are minuscule magnets.

It follows and is also increasingly apparent that these external fluctuations in magnetic fields can affect virtually every circuit in the biological machinery to a lesser or greater degree, depending both on the particular biological system and on the particular properties of the magnetic fluctuations.

Chronoastrobiological studies are contributing to basic science – that is, our understanding is being expanded as we recognize heretofore unelaborated linkages of life to the complex dynamics of the sun, and even to heretofore unelaborated evolutionary phenomena. Once, one might have thought of solar storms as mere transient ‘perturbations’ to biology, with no lasting importance. Now we are on the brink of understanding that solar turbulences have played a role in shaping endogenous physiological chronomes. There is even documentation for correlations between solar magnetic cycles and psychological swings, eras of belligerence and of certain expressions of sacred or religious feelings.

Chronoastrobiology can surely contribute to practical applications as well as to basic science. It can help develop refinements in our ability to live safely in outer space, where for example at the distance of the moon the magnetic influences of the sun will have an effect upon humans unshielded by the earth's native magnetic field. We should be better able to understand these influences as physiological and mechanical challenges, and to improve our estimations of the effects of exposure.

Chronoastrobiology moreover holds great promise in broadening our perspectives and powers in medicine and public health right here upon the surface of the earth. Even the potential relevance of chronoastrobiology for practical environmental and agricultural challenges cannot be ruled out at this early stage in our understanding of the apparently ubiquitous effects of magnetism and hence perhaps of solar magnetism on life.

Geologists are concerned that the earth's magnetic field is waning or even collapsing, and if this trend continues it might be as much as centuries before this umbrella protection from solar winds is gone. Yet it is possible that generations in the near or far future might look back and be grateful that our generation was looking ahead to their welfare so that they could know what to expect and would have time to prepare for their safety.

In the subsequent chapters the problems chronobiology, chronocardiology, and chronoastrobiology will be considered.

CHRONOBIOLOGY

Living organisms on this planet have adapted to the daily rotation of the earth on its axis. By means of endogenous circadian clocks that can be synchronized to the daily and seasonal changes in external time cues, most notably light and temperature, life forms anticipate environmental transitions, perform activities at biologically advantageous times during the day, and undergo characteristic seasonal responses.

Half a century ago, the birth of chronobiology as a science sui generis came about to a large extent due to F. Halberg's demonstration of free-running. In mice, in the absence of the eyes, variables ranging from core temperature to hepatic glycogen content and serum corticosterone continued to cycle with a period close to but statistically significantly different from 24 hours [1,2]. The circadian period differed among animals and among different variables in the same individual. This finding provided a basis for the endogenicity of rhythms in general and for the adrenal cycle in particular. Today, the genetic basis of circadian rhythms is no longer disputed [3]. Thus, fos family genes have been reported to exhibit differences in their specific expression patterns in the suprachiasmatic nuclei; photic and intrinsic circadian coordination may reside in separate cell populations in the ventrolateral and dorsomedial subdivisions [4], allowing for cell specificity of their respective circadian function(s).

Endogenous circadian rhythms have been described in a wide range of organisms from prokaryotes to man. Although basic circadian mechanisms at the molecular level are genetically fixed, certain properties of circadian rhythms at the organismic level can be modified by environmental conditions and subsequently retained for some time, even in organisms shielded from 24-hr environmental variations.

The circadian rhythmicity of eukaroytic organisms is dictated by an innate program that specifies the time course through the day of many aspects of metabolism and behavior. The programmed sequence of events in each cycle of the rhythm has been evolved to parallel the sequence of predictable change (physical and biological) in the course of the day-outside: ii constitutes an appropriate day-within. It is a characteristic, almost defining, feature of these circadian programs that their time course is stabilized with almost clocklike precision to parallel the stable time course of the environmental day. There is equally clear functional significance to the program's being driven by a self-sustaining oscillator; thus, the program is subject to entrainment by one or more of the external cycles whose period it closely approximates.

While the vast literature on the molecular genetic basis of rhythms focuses almost exclusively on the details of the circadian system, a few studies suggest a molecular basis for circadian, ultradian and infradian rhythms as well.

The circadian system - that basis, due to which are shown integrative activity and regulating role neuroendocrinal system which is carrying out the exact and thin adaptation organism to constantly varying environment conditions [5, 6**].** As in other vertebrates, the human circadian system is characterized by a distinct temporal order of its components. This order is maintained by the coupling forces between various oscillators as well as by the entraining signals from the zeitgebers.

R.J. Konopka et al. [7] in particular have followed upon earlier work by C.P. Kyriacou and Hall [8], revealing that the period gene in *Drosophila melanogaster* coordinates not only circadian rhythms associated with adult emergence and behavior, but also a much higher frequency rhythm that accompanies the male's courtship song. About 1-min oscillations in the rate of sound production reportedly, in turn, are sped up, slowed down, or seemingly eliminated in three "per" mutants, an extension from "clock" to "chronome". It has also been suggested that infradians may emerge from a weak coupling of a circadian "clock" gene with its environment.

That infradian components also have a molecular genetic basis is likely from work on plants, when built-in photoperiodic aspects of responses in plants include flowering that is day-length-dependent [9-11]. Work on *C. elegans* further analyzes a molecular genetic basis to embryonic development possibly related chemically to the circadian system, while the heterochronic gene LIN 42 oscillates apparently with an ultradian (reportedly about 6-hour) component [12]. F. Halberg's [13] noted on a broader-than-circadian time structure, that includes trends with age as well as disease risk, is thereby vindicated at the molecular level. The concept of chronomes (much broader than clocks) is bound to prevail if concern for them leads to the difference between delaying rather than accelerating malignant growth.

The infradian rhythms (with the period is longer circadian) are found out in organism of the man and animals inherent to many physiological processes (fig. 1). It is rather probable, that they also have endogenic nature and serve one of the mechanisms ensuring coordinated physiological systems activity reorganization during organism adaptation to the environment. Now study the circaseptal (about 7-day's) rhythms attracts special attention of the researchers.

The circaseptal rhythmicity in physiological parameters of the man quite often communicates extremely with the social reasons (calendar week). Really, the period of 7 days should inevitably be present at the data of medical statistics. However, basic contribution to the circaseptal rhythmicity is brought in by ecological changes, in particular, connected with the sector structure of an interplanetary magnetic field.

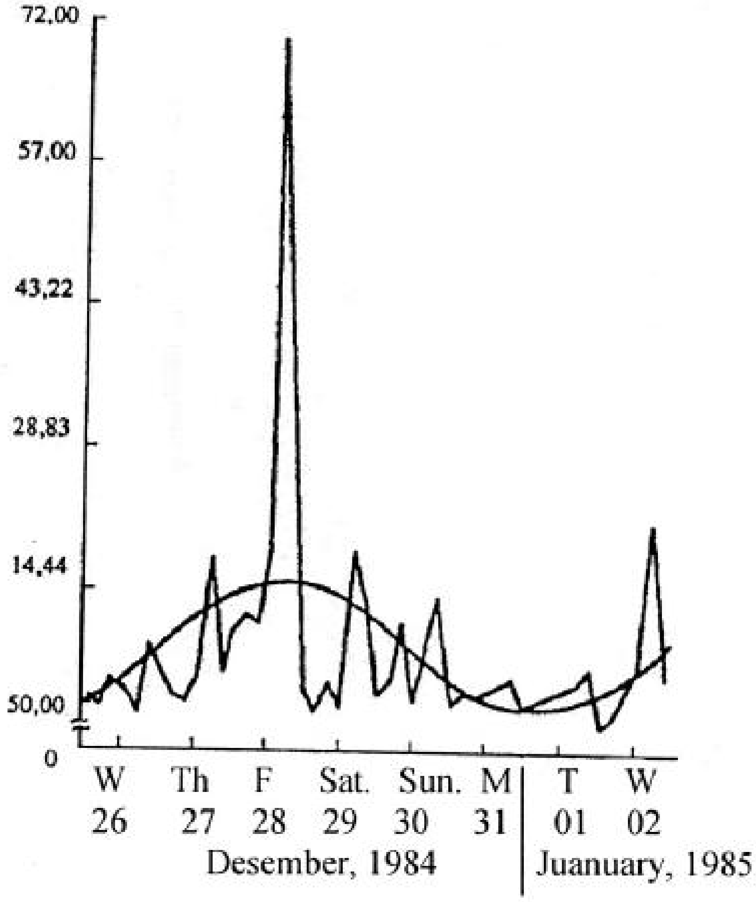


Fig. 1. Daily and week rhythms of the melatonin concentration in pineal gland rats [by F.I. Komarov er al., 1994].

Nearly half a century after showing the effect of light upon rhythms at different levels of organization, F. Halberg's insight has led him back to realize the importance of understanding and assessing also non-photic environmental influences on biota Still a controversial topic, it may nonetheless prove to be a critical one, primarily at a time when humans are getting ready for long journeys into space, away from hospitals. Any untoward effects from non-photic solar effects, perhaps on individuals who may be more susceptible at the outset by virtue of alterations in the variability of their BP or HR within the physiological range, warrant immediate attention so that countermeasures may be applied preventively.

The purpose F. Halberg [1, 14-17] researchs are not to recount the early discoveries of the endogenicity of the circadian adrenal cortical cycle, based on the free-running of circadian and other "circa" rhythms in (genetically) blind mice (born anophthalmic) [2, 18-20] and blinded mice (with surgery removing the transducer of light) [21], or in the absence of dominant environmental synchronizers such as the lighting regimen or mealtime, or a diet restricted in calories [21-23]. It is not to emphasize how the sequential phase relationship of circadian cellular rhythms, the labeling of phospholipid and the formation of hepatic RNA preceding that of DNA [19, 24] may shed light on life's origins, or to demonstrate the important clinical implications of the difference in outcome, life or death, from a variety of stimuli (noise, endotoxins or drugs) [25-28], or the rules of schedule shifts [21, 22, 24, 29-31]. It is not to enumerate each new rhythm added to the existing body of knowledge [15, 21, 32], or even to list multifrequency rhythms responsible for the chronomodulations [feedsidewards] that underlie the difference between the stimulation or inhibition of DNA synthesis [33] or cancer growth [34, 35] or the difference between life and death in response to the same dose of the same molecule [36]. Nor is it to document the early indirect evidence for an endogenous organismic time structure based on free-running [26, 27, 29, 31], notably in objectively quantified isolation studies [37-39] and on work on human twins reared apart [40], or to review the evidence for the synchronizing role of the socioecologic setting [20] that underlies the amenability of rhythms to change their temporal location in relation to environmental cycles, according to specific rules of adjustment. An account of these early developments is reviewed elsewhere [41].

Circadian pacemakers in many animals are compound. In rodents, a two-oscillator model of the pacemaker composed of an evening (E) and a morning (M) oscillator has been proposed based on the phenomenon of "splitting" and bimodal activity peaks [42]. The authors describe computer simulations of the pacemaker in tau mutant hamsters viewed as a system of mutually coupled E and M oscillators. These mutant animals exhibit normal type 1 PRCs when released into DD but make a transition to a type 0 PRC when held for many weeks in DD. The two-oscillator model describes particularly well some recent behavioral experiments on these hamsters. The authors sought to determine the relationships between oscillator amplitude, period, PRC, and activity duration through computer simulations. Two complementary approaches proved useful for analyzing weakly coupled oscillator systems. The authors adopted a "distinct oscillators" view when considering the component E and M oscillators and a "system" view when considering the system as a whole. For strongly coupled systems, only the system view is appropriate. The simulations lead the authors to two primary conjectures: (1) the total amplitude of the pacemaker system in tau mutant hamsters is less than in the wild-type animals, and (2) the coupling between the unit E and M oscillators is weakened during continuous exposure of hamsters to DD. As coupling strength decreases, activity duration (alpha) increases due to a greater phase difference between E and M. At the same time, the total amplitude of the system decreases, causing an increase in observable PRC amplitudes. Reduced coupling also increases the relative autonomy of the unit oscillators. The relatively autonomous phase shifts of E and M oscillators can account for both immediate compression and expansion of activity bands in tau mutant and wild-type hamsters subjected to light pulses [42].

In the whole hypotheses about uniform internal clocks and polioscillator of temporary structure organism are quite compatible. The biorhythms in many respects are incorporated in the genetic organism program. The connection of separate rhythms with external oscillator of time can be a straight line, more or less strong. In a number of cases the factors of external environment only trigger the certain rhythmic activity.

Ontogeny is the life history of the individual organism, including its physical construction from a fertilized egg, the functional maturation of its behavioral, homeostatic and reproductive systems, and the decline of these systems with age. Because so many functions – behavioral, physiological, and biochemical – within an individual organism show circadian rhythmicity, the ontogeny of any particular function is likely to include the appearance of and changes in its rhythmic control.

The circadian rhythm is a term used to define the chemical and biological oscillations that occur daily in most species including humans. These circadian responses are primarily triggered by visible light impinging on non-visual photoreceptors in the retina, which is then directed to the suprachiasmatic nucleus (SCN) in the hypothalamus. This leads to a cascade of hormonal changes in the pituitary, pineal, adrenal and thyroid glands. The lack of light, total darkness, blocks some of these hormonal events while enhances its own cascade of neuroendocrine changes. This daily oscillation of darkness and light has a profound effect on most physiological functions in the body.

Chronobiological research shows that the axis between the SCN and the paraventricular nucleus of the hypothalamus is crucial for the organization/synchronization of the neuroendocrine and autonomic nervous system with the time of day. This SCN-neuroendocrine the paraventricular nucleus of the hypothalamus axis takes care of a timely hormonal secretion. At the same time, the SCN-autonomic the paraventricular nucleus of the hypothalamus axis fine-tunes the organs by means of the autonomic nervous system for the reception of these hormones. Finally, the similar organization of the projections of the human SCN as compared with that in the rodent brain suggests that these basic principles of neuroendocrine autonomic interaction may also be true in the human. The physiological data collected in humans thus far seem to support this hypothesis, while pathological changes in the SCN of humans suffering from depression or hypertension indicate a role for the SCN in the etiology of these diseases.

The mammalian circadian oscillator, located in the suprachiasmatic nuclei of the anterior hypothalamus, serves as the principal source of rhythmic temporal information for virtually all the physiologic processes in the organism, including the alternating expression of sleep and wakefulness.

The pineal gland, as one of the most significant components of the songbird circadian pacemaker, not only has the capacity to autonomously produce circadian rhythms of melatonin release but also is capable of storing biologically meaningful information experienced during previous cycles.

N.A. Agadzhanyan et al. [43] has developed the neuroendocrine mechanism regulation and control circadian rhythmicity of the physiological functions in the body (fig. 2).

F. Halberg [1, 3, 7] already noted that for chronobiology to evolve as a science, it was necessary to document the ubiquity of rhythms, to demonstrate their critical importance, and to develop the methods for their assessment and their interpretation. His work helped several generations of chronobiologists worldwide who have in one way or another been associated with F. Halberg

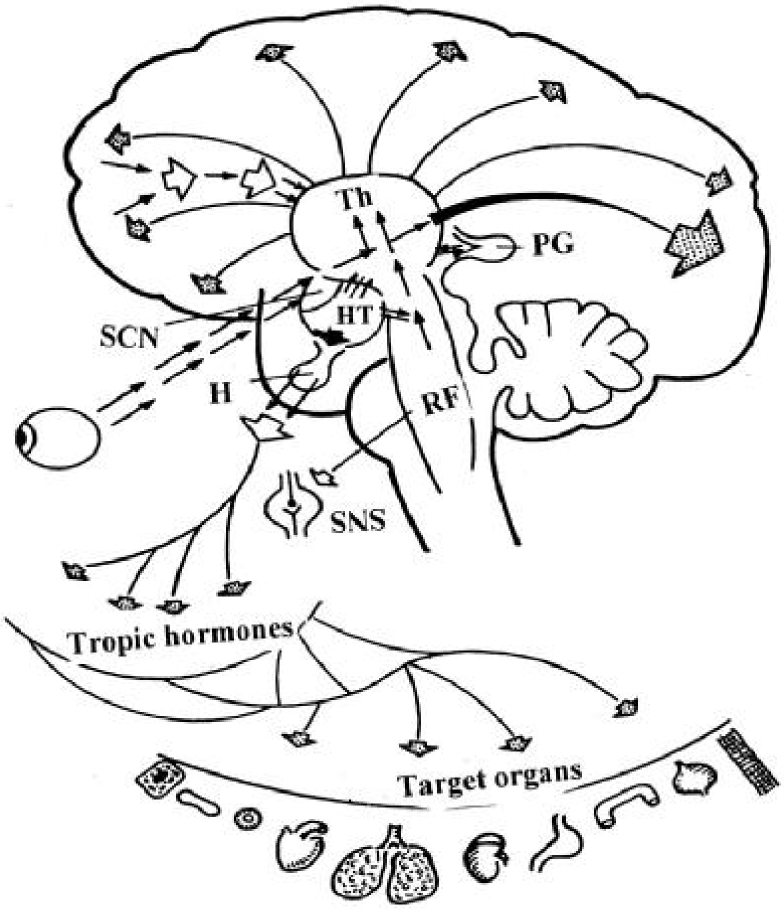


Fig. 2. Neuroendocrine mechanisms regulation and control of the circadian rhythmicity physiological functions in the body.

SCN – Suprachiasmatic nucleus; Th - Thalamus; H – Hipophysis; PG – Pineal gland; RF – Reticular formation; SNS – Sympathetic nervous system; HT- Hypothalamus.

and have contributed to what quantitative chronobiology is today, the pitfalls of a time-irivariant physiology have been identified and the limiting view of homeostasis replaced by that of a partly built-in time structure (chronome) in health.

The received results testify that circadian rhythms are endogen oscillators practically of all physiological functions and biochemical reactions of organism. The stability endogen component of internal clocks is created by interaction of nervous and endocrinal system.

Circadian systems direct many metabolic parameters and, at the same time, they appear to be exquisitely shielded from metabolic variations. Although the recent decade of circadian research has brought insights into how circadian periodicity may be generated at the molecular level, little is known about the relationship between this molecular feedback loop and metabolism both at the cellular and at the organismic level [44].

The endogenal rhythmicity has in the basis difficult dynamics of biological energy. It is redistributed and circulates in body 12 meridians. It is considered, that general harmonization of ability to live is reached due to the constant circulation of internal energy on these meridians.

A.A. Marjanovky (2003) has developed the circuit circadian rhythms of daily activity acupuncture meridians (fig. 3). The maximal energy in one of the meridians corresponds, minimal in its opposite one [43]. Thus, each meridian has the time of activity and time of rest.

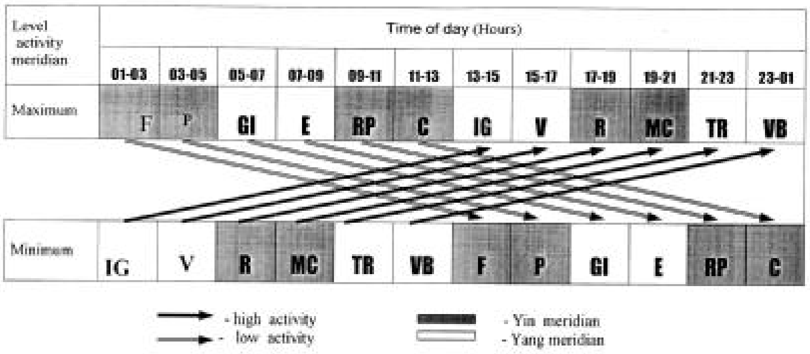


Fig. 3. Circadian rhythm of activity acupuncture meridians.

Central to the new discipline is the concept of chronomes, broad time structures in us and around us, which F. Halberg formulated explicitly following a session on chronobiology organized by the late Norberto Montalbetti at the XIV International Congress of Clinical Chemistry in San Francisco (July 22-26, 1990) [45, 46]. It led to the new field of chronomics [47], the mapping of chronomes, providing the needed foundation for future inroads in the dynamics of life.

Not only is hypothesis testing on more than one chronome component essential, so is parameter estimation. Visual inspection is insufficient to reliably appraise the information contained in a data set. By contrast, chronobiological analyses may resolve variability within the physiological range while also yielding information about any environmental influence and/or the endogenous nature of rhythms. It is no surprise that F.

Halberg introduced the periodogram [19, 48] and power spectrum [49, 50] into what became chronobiology, further developing a series of statistical procedures, of which the single cosinor [51] is perhaps the most widely disseminated.

Individual rhythm characteristics for each variable were summarized for the group by population mean cosinor. The vast majority of variables revealed statistically significant within-day changes in values as validated by one-way ANOVA. All vital signs (except for intraocular pressures) and all serum hormones displayed a prominent circadian rhythm for the group, as did most variables in whole blood, while only about half of the variables in urine demonstrated a significant group rhythm. The results obtained are meant to: (a) document the circadian time structure; and (b) serve as reference values for circadian rhythm characteristics (range of change, mesor, amplitude and acrophase) for a defined group of individuals: clinically-healthy adult men in the prime of life.

The most important aspect of human circadian physiology that limits adaptation to the extreme schedules inherent in shiftwork and jet travel is the primacy of light among entraining signals, or zeitgebers. Exposure to sunlight for night shiftworkers, or for jet travelers at their destination, results in maintenance (or resetting) of the clock to environmental time. This response can be prevented or overridden with extraordinary avoidance of sunlight or with provision of artificial light of sufficient duration and intensity to negate the sunlight signal, an approach shown to be effective in the treatment of shiftwork sleep disruption. Practical issues sharply limit the application of artificial lighting to all shiftwork settings, however, and the role for a pharmacological chronobiotic agent capable of accomplishing the same end is potentially very large.

The majority of physiological parameters finds out constant deviations from their average meaning and organism aspires not to absolute stable function, and to deduct them in the certain adequate limits at continuous fluctuations of absolute sizes. It enables to save a steady condition, and at the necessary moment of external environment change allows to choose meanings, adequate for the necessary situation. Therefore circadian fluctuation of physiological functions parameters, in particular breath, ones reflects the valid picture of system activity as a whole and its adaptive opportunities.

The renin-angiotensin-aldosterone system (RAAS) is characterized by a circadian rhythm whose acrophase is detectable early in the morning. The prorenin and angiotensin converting enzyme show a circadian rhythm as well. However, while the prorenin is in phase with the RAAS the angiotensin converting enzyme shows its circadian acrophase in the afternoon suggesting a negative feed-back. The RAAS circadian rhythm is influenced by many factors. Its mesor is modified by sodium intake. The physical activity and rest affect both the mesor and acrophase. The variations in mesor amplitude and acrophase in aged subjects are conditioned by sex and physical activity. Moreover, the RAAS circadian rhythm seems to be influenced by the race. In addition, it is abolished by the beta-adrenergic blockade, suggesting the existence of an adrenergic clock. Interestingly, the RAAS circadian rhythm seems not to be a pacemaker for the blood pressure circadian rhythm, whose acrophase is early in the afternoon. The RAAS circadian rhythm is not substantially modified has in essential hypertension. However, the circadian rhythm of plasma renin activity is disappeared in the low-renin essential hypertension, while the circadian rhythm of plasma aldosterone is detectable. On the contrary, the aldosterone circadian rhythm is not detectable in ascitic liver cirrhosis; but, it is restored when the ascites is removed by peritoneal-jugular shunt. No significant variation of the RAAS circadian rhythm seems to occur in obesity and Cushing's syndrome. The RAAS circadian rhythm has disappeared in Conn's disease as well as in Bartter's syndrome and Liddle's syndrome. The administration of indomethacine in Bartter's syndrome and of triamterene in Liddle's syndrome is able to restore the RAAS circadian rhythm. Finally, the RAAS circadian rhythm is not detectable in the heart or kidney transplanted patients; such a phenomenon could be attributed to cyclosporine and corticosteroids administration and to the denervation of the transplanted organs [55].

I.V. Radysh [52] noted that the circadian acrophases of the breath parameters in the men among were at 12-21 hr, and batyphase – at 02-05 hr; the women in follicular phase – in the day time, and lutein – in the evening, batyphase – the night in the both phases of menstrual cycle. The facts during the dream of the breath ventilation decrease mainly at the expense of respiratory volume reduction and insignificant frequency breath changes are observed in the work of the other researchers.

O.N. Ragosin [53] noted that the chronotherapy of melatonin for the patients bronchial asthma resulted in restoration of circadian structure rhythms bronchial passableness (fig. 4). Thus, the phase parameters of rhythms bronchial passableness are synchronized as concerning time of day, and among themselves, i.e. there is a distinct acrophase displacement of bronchial rhythms parameters passableness concerning reduction of their caliber in the evening time. The author considers, that the synchronizing effect of reception melatonin, shown in correction of external breath phase structure rhythms, testifies to the important role of the central rhythmogenesis mechanisms in the pathogens of the bronchial asthma.

In realization of adaptive organism reorganizations important meaning is placed on the water-minerals exchange, in particular the function excreation of kidneys.

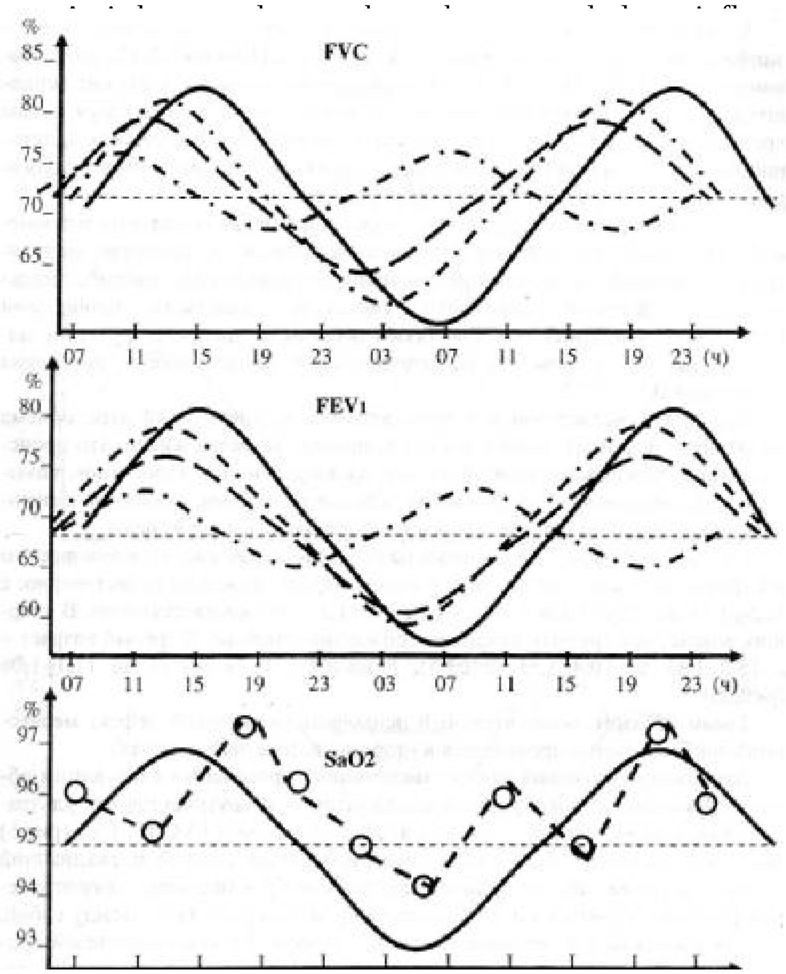


Fig. 4. Chronogram of function external breath rhythms parameters and SaO_2 in the patients with bronchial asthma on background chronotherapy of melatonin.

O – – now rhythm; ——— after melatonin;

...... 2-h rhythm; — — 16-h rhythm; — · — · 24-h rhythm

Seasonal variability urine elements in the children of early age testifies that the maximal concentration of Na was observed in the winter, K and Ca - in autumn, and Mg – in summer [54].

Chronobiological research shows that the practically healthy young women's circadian rhythms acrophase urine excreation of elenents: in case of K in follicular phase is 16 h 46 min, Na - at 16 h 56 min, Mg - at 15 h 30 min and Ca - at 19 h 23 min, and in lutein phase, accordingly, 14 h 08 min, 17 h 52 min, 17 h 49 min and 20 h 36 min were observed at 12 h, thus batyphase - from 01 till 07 hr irrespective phases of menstrual cycle (fig. 5).

Chronobiological research shows that many pathological functions are accompanied by disorders, a temporal organization of physiological functions of body. At the same time, biorhythmologycal and systems approaches have not yet been applied to the study of a stress complexly.

According to the research results, authentic rhythms of corticosterone and minerals contained in blood of the intact animals make 80 %, and excreation of minerals and urine make 74 %. At the same time, the authentic rhythms are dominated by circadian rhythms (for blood and urine indices – 75 % and 91 % respectively). The intact animals blood minerals rhythm amplitude/mesor ratio is smaller than that of urine. Due to the extensive range of fluctuations of mineral and urine excreation, their fluctuation in blood plasma are smaller.

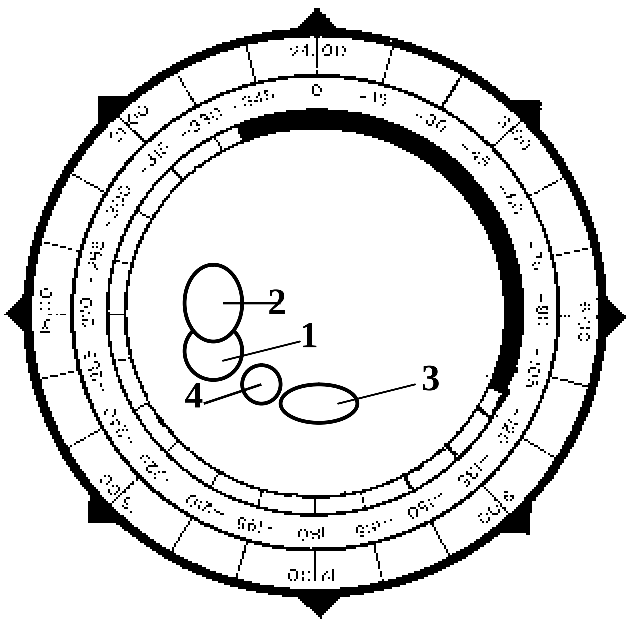


Fig. 5. Cosinor the urine excretion Na (1) and K (3) in the follicular phase; Na (2) and K (4) in the lutein phase of menstrual cycle in the healthy women.

Generalizing the data of rhythmological research of water – mineral system, one can draw the following conclusion: that the majority of intact animals are characterized by circadian rhythms of water – mineral homeostasis with internal synchronization of a period between rhythms of individual indices and rhythms having a certain value of mesors and amplitudes. Rhythms acrophases bear individual character and equivodcal (that is uncertain in character). At the same time, one should note that there is a 6 – 12 hours difference between acrophases of the same water – mineral homeostasis indice in in the plasma of blood and urine.

Under the influence of long – duration stress – factors a water – mineral system reorganizes a temporal structure of functions of its parts**,** this system exists in a transformation of circadian period into nonperiodical (irregular) fluctuations, or in a formation of mainly infradian rhythms (for blood and urine indices – 56 % and 54 % respectively), and circa- and ultradian rhythms respectively make 21, 27% and 23, 19% ; values of some mesors and amplitudes undergo changes. At the same time, the authentic rhythms of corticisterone are in infradian range in all cases, and it has been statistically proved that the corticosterone mesor and amplitude are greater than that of intact animals ($P<0.01$), that is a relatively constant concentration of mineral in extra- and intracellucar space of an organism that does not undergo changes.

Comparing the data of literature with our results, one can suppose that neuroendocrinal changes, and probably their temporal structure changes, result in the fact that both circadian chronostructure of sodium, potassium, copper and zinc excretion, and confidence intervals of fluctuations of their mesors and amplitudes undergo changes.

The research results give reason to consider the complex of water-saline homeostatic system reactions to be a defense reaction to effects of damaging factors. Their essence exists in a reorganization of circadian rhythmic of a system. In different components of water-saline system the reorganization bears equivocal character. So, the rhythmic of water-saline homeostasis of blood is characterized by changes of only a period and amplitude, and an efferent component is characterized by changes of a period, mesor and amplitude. Logically, one can suppose that due to excessive lability of water-saline system efferent component rhythms parameters. It is the constancy of blood water-saline homeostasis rhythms of the indices and the high degree of the executive apparatus lability rhythms parameters that make the water-saline system a precise mechanism providing stability of organism water-saline homeostasis indices under the influence of damaging factors on the basis of a self-regulation principle.

The infra-, circa- and ultradian rhythms, which we have determined, and also non-periodical fluctuations, give us a reason to consider reactions of water-mineral system of the animals to stress effects to be individual.

So, the research has made it possible to determine peculiar features of circadian organization of a water-mineral system and more detailed mechanism of its ability to resist damaging factors in the conditions of experimental stress.

Thus, the rhythmic fluctuations of the various biological phenomena and functions of body form uniform ensemble, in which the strictly ordered sequence in activation metabolic, physiological and behavioristic processes is visible. In a basis of temporary rhythms coordination lays principle according to which the fluctuations of the various organism level of functioning systems are synchronized on the phase of rhythms functionalities of these systems.

The problems of chronobiology get the special urgency in present period in connection with migration processes, active development of new extreme regions and also introduction of this science achievement in medical practice, in biotechnology and other branches of biology.

In the subsequent chapters the questions of chronocardiology interaction will be considered.

CHRONOCARDIOLOGY

Recently we notice progress in the study of the chronobiological aspects of the cardiovascular system. Results of these studies confirm that most cardiovascular physiological parameters (such as heart rate, blood pressure, electrocardiogram indices) and pathophysiological events (myocardial ischemia/infarction, sudden cardiac death) show circadian rhythms. Results also suggest that consideration of these rhythms is important for the diagnosis and treatment of cardiovascular disorders and that restoration of normal circadian rhythms may be associated with clinical improvement. Thus, the study of circadian rhythms in the cardiovascular system is emerging as an important area of investigation because of its potential implications for patient management [56].

It is necessary to notice, that the severe rhythm of heart work is the main attribute of its normal condition. Circadian rhythm parameters the heart rate (HR) of activity the first time was established at the end of XIX century by Zadek.

Chronobiological research shows that the clinically healthy persons ranging in age from 18 to 46 years of inside group has circadian rhythm of heart rate. As a rule, circadian rhythm acrophases are allocated in an interval 12-20 h, and batyphases - in an interval 02-06 h. Thus the daily heart rate amplitude was observed in limits from 9 up to 24 beats per min [43, 52].

R.M. Zaslavskaya [57] hoted that at 96,4% clinically healthy persons have the day time type of circadian rhythm heart rate. This type of a rhythm was colled day time was characterized by registration acrophase in the period of active being awake from 07 till 22 o'clock. The night type of rhythm differed acrophase in the period of night - from 22 till 07 o'clock.

Chronobiological research shows that the change of parameters autocorrelogram testified the stationary increase of process in light time of day with relative reduction in dark. These attributes specified increase that the heart rhythm central parts regulation of influence in the afternoon and reduction of their activity at night with prevailing autoregulation action of managment contour. The day time of rhythmogram were characterized by small disorder in duration R-R intervals and absence of respiratory waves. In night time their dispersion was increased, there were respiratory waves (Table 1).

As usually, the heart activity changes proceed with simultaneous change of a vascular condition, that is in reply to the certain changes in external environment the shifts in the whele cardiovascular system are observed.

TABLE 1: Circadian rhythm parameters of heart rate variability

Parameter	Mesor	Amplitude	Acrophase, h, min
Mo, sec	0,877±0,004	0,082±0,007	03,27
AMo, %	38,08±0,18	3,41±0,23	15,57
Δ R-R, sec	0,253±0,001	0,042±0,007	04,51
SI	86,3±1,1	26,7±1,4	16,45

Mo: mode;
AMo: amplitude of mode
SI – stress index

K. Otsuka [58] noted that a physical activity showed a circasemiseptan and circaseptan periodicity as well as the circadian component, especially in subjects with an irregular sleep-wakefulness life style. On the average, physical activity was greater on a working day than on a holiday. Everyday physical activity reflects in part the ability to exercise, and it is expected that this actometer can contribute or provide an objective individualized quality-of-life index. The effect of physical activity on circadian profiles of blood pressure (BP), HR and HR variability is also examined. Autors observed that BP started to increase several hours before getting up. This fact likely shows that there is an endogenous circadian rhythm in BP, independently of the sleep-wakefulness cycle. Lastly, they investigated the relationship between physical activity and HR in patients permanently paced; they confirmed that the DDDR pacing mode was more physiological than the VVI or VVIR mode. This newly developed actometer will bring about further progress in chronobiology.

Other authors the study clinically healthy Japanese, ranging in age from 12 to 83 years, who were monitored in their electrocardiogram over the day-night span. An opposite age-related trend was detected for two properties of sinusal R-R intervals circadian rhythm, i.e., mesor (positive trend) and amplitude (negative trend). Accordingly, the sinusal R-R intervals circadian rhythm can be classified as an "amphiclinous rhythm", i.e., a rhythm in which the cardiac interbeat duration shows a progressive increase of its daily mean value along with a progressive deamplification of its oscillatory extent. Furthermore, the rhythm is characterized by a progressive anticipation in time of its oscillatory maximum of duration with advancing age. The findings suggest that the biological clocks regulating the HR circadian rhythm in human beings undergo a resetting of their mechanisms of tonic, amplitude and phasic modulation as a function of age. The clock-mediated readjustment of the HR circadian rhythm may be regarded as one of the mechanisms for explaining the bradycardia that is associated with the aging process in human beings [61].

In these years, circadian periodicity in the onset of myocardial ischemia, myocardial infarction, sudden cardiac death and ischemic stroke has been confirmed by several investigators. There has also been reported that there exists a significant circadian rhythm in ventricular arrhythmias in patients with myocardial infarction. These recent advances in chronocardiology depend on a development of a high quality built-in A/D converter in ambulatory ECG monitoring system and a remarkably developed sophisticated software. One of the most current topics in recent years is heart rate variability. As an index of HR variability, RR50 is frequently estimated by the cosine fitting technique [59]. Next, the authors analyzed the so-called Lorenz plot for another index of HR variability, that is preceding R-R intervals and coupling intervals were plotted sequentially every 3 hours on the abscissa and ordinate, respectively. Finally, the authors investigated HR variability by power spectral analysis of R-R intervals both by the maximum entropy method and the fast Fourier transform. Mainly, the authors introduced current topics in HR variability, but recent advances in ambulatory blood pressure (BP) monitoring system are also strikingly remarkable. The newly developed monitoring system of physical activity donated quite a few informations evaluating episodic changes of HR and BP. This device was also useful for finding out the difference between the individual life styles, such as the eveningness versus morningness [59].

Curione M. at al. [60] has been reported that study estimates the unpredictable disorder (chaos) within the 24 h pattern of sinus R-R intervals (SRRI) in clinically healthy pregnant women (CHPW) and clinically healthy non-pregnant women (CHNPW), in order to evaluate the early gestational changes in neurovegetative cardiac pacing. Both the SRRI and entropy were tested via the Cosinor method to better decipher whether or not the periodic disorder in heart rate variability is modified in pregnancy as a result of a gestational tonic resetting of the cardiac sympatho-vagal regulation. Cosinor analysis documented that the circadian rhythm of both the SRRI and entropy were preserved in CHNPW and CHPW. However, the circadian rhythm of SRRI and entropy in CHPW exhibited a significantly decreased 24 h mean. Via the analysis of the rhythmicity of entropy, this study has documented that the chaos in the 24 h pattern of SRRI is less prominent in CHPW than in CHNPW. Such a reduction of level in the deterministic periodic chaos of heart rate variability provides evidence that, in early pregnancy, a tonic elevation of the sympathetic activity regulates cardiac pacing.

The circadian rhythm of blood pressure is not a passive consequence of the impact of exogenous factors. Endogenous mechanisms play an important role in the generation and maintenance of BP rhythm. The adaptation of the exogenous components of BP rhythm to the demands of the environment is modulated by the circadian-time-dependent responsiveness of the biologic oscillator. A neuronal network in the rostral hypothalamus including the suprachiasmatic nucleus is implicated in the generation of BP rhythm, in the modification of the rhythm amplitude (possibly due to homeostatic constraints), and in the regulation of its phase. The central sympathoexcitatory pathway to the upper thoracic cord plays a crucial role in the maintenance of normal circadian BP rhythm. The circadian pattern of BP is influenced also by hormonal factors such as the hypothalamic-pituitary-adrenal and the hypothalamic-pituitary-thyroid axes, the renin-angiotensin-aldosterone system, opioids, and various vasoactive peptides.

I.V. Radysh [52] has reported that the clinically healthy men, ranging in age from 18 to 28 years, circadian acrophase of sistolic blood pressure (SBP) and mean blood pressure (MAP) there were in an interval 13-19 h, diastolic blood pressure (DBP) - 18-22 hours (fig. 6). The amplitude circadian fluctuations of SBP reached 20 mm Hg, and DBP and SBP - 15 and 9, accordingly.

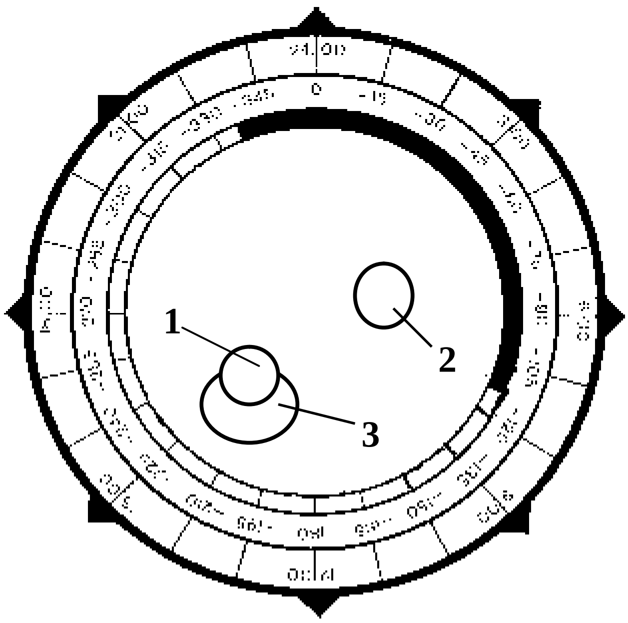


Fig. 6. Cosinor the circadian rhythm of SBP (1), DBP(2) and MAP (3) in the clinically healthy men.

R.M. Zaslavskaya [62] noted that after examining clinically healthy persons the circadian acrophase SBP with at 15 h 54 min was observed among 94,5 %-day's types circadian rhythm. The day time type of a daily rhythm SBP with acrophase at 15 h 24 min was prevailing. Thus the author has revealed a day time type a daily rhythm DBP only among 43,6% and night - among 56,4% surveyed.

Chronobiological research shows that the clinically healthy women, ranging in age from 18 to 26 years, have the circadian acrophase of blood pressure at afternoon and evening time [52]. The sportswoman have circadian acrophase SBP at 12-15 h, and DBP - 23-02 h [63].

In various phases of menstrual cycle the difference in mesor BP is only marked, circadian rhythm acrophases come synchronously, thus the amplitude is higher in follicular phase (Table 2) [52].

The circadian variations of BP depend on physiological state-sleep and wakefulness, pregnancy, work, and senescence (primary aging). In some essential hypertensive patients and in patients with secondary hypertension the nocturnal fall in AP is reduced or absent (nondippers). Target-organ damage is more advanced in nondippers than in dippers. The occurrence of cardiovascular events exhibits a prominent circadian pattern, with events more frequent in the morning (06-12 h).

The sphygmochron is a computer summary of results from chronobiological analyses performed on BP and HR data collected around the clock, preferably by ambulatory monitoring. It consists of two approaches, one parametric (model-dependent), the other non-parametric (model-independent). The parametric approach entails the least-squares fit of a two-component model consisting of cosine curves with periods of 24 and 12 hours. Estimates are obtained for the MESOR (midline-estimating statistic of rhythm), a rhythm-adjusted mean, and for the amplitude and (acro)phase of each component, measures of (half) the extent of predictable change within a cycle, and of the timing of overall high values recurring in each cycle, respectively.

TABLE 2:Circadian rhythm of blood pressure in the clinically healthy women

Parameter	Phase MC	Mesor	Amplitude	Acrophase, h, min
SBP, mm Hg	1	113,1±0,1 ***	7,76±0,45	15,46
	2	110,2±0,1	6,21±0,33	17,34
DBP, mm Hg	1	73,3±0,1 ***	4,84±0,19	19,08
	2	68,9±0,1	3,44±0,29	21,13
MAP, mm Hg	1	86,6±0,08 ***	5,64±0,20	16,19
	2	83,3±0,14	4,53±0,34	18,51

SBP: sistolic blood pressure;

DBP: diastolic blood pressure;

MAP: diastolic blood pressure;

MC: menstrual cycle.

1 – follicular phase; 2 – lutein phase

*** p<0,001

To circumvent any limitations of the parametric approach based on a model that may not invariably suffice to appropriately describe the circadian pattern, the analyses include a nonparametric approach, based on stacking the data over an idealized cycle. It was deemed desirable since it was readily understood and could serve as a guide for timing treatment. It can serve as a complement to adjusting the model by the choice of different harmonic terms for each profile. Despite the merits of improving each individual fit, it was felt important to standardize the model, so that reference values could be derived for each parameter of the model. The given subject's rhythm characteristics could then readily be compared with those of peers. Values outside the norms could then become putative risk indicators.

In the nonparametric approach, the subject's data are compared by computer to the time-varying upper 95% prediction limit (chronodesm) of clinically healthy peers, matched by gender, age and ethnicity. Instead of asking only whether a BP value is too high or acceptable, this approach answers more complete and often more pertinent questions, such as "For what percentage of the 24-hour day are the subject's BP readings above the chronodesmic limit?", "By how much is the BP excessive ?" (gauged by the "area under the curve", delineated by the subject's profile when it exceeds the limit and the limit itself; expressed in mm Hg x hour during 24 hours), and "When does most of the excess occur ?". Years later, part of this "hyperbaric index" (HBI) concept was copied to assess a BP load, with the shortcomings, however, that the BP load considers only the percentage time elevation and not the "area under the curve", and that it uses time, gender, age, and ethnicity-unqualified fixed limits as reference [64, 65]. Elsewhere, the advantages of the HBI over the BP load are illustrated by a comparison of patients seen at the Mayo

Clinic who have very similar BP loads but drastically different HBIs [66].

In addition to the time-specified reference limits for the interpretation of time-measurements, reference limits were also derived for the interpretation of the circadian rhythm characteristics. If the BP MESOR exceeds the upper 95% prediction limit, MESOR-hypertension is diagnosed; if the circadian amplitude is excessive, CHAT circadian hyper-amplitude-tension) is diagnosed; and if the circadian acrophase occurs at an odd time, circadian ecphasia is diagnosed.

Analyses of long time series [67-76] yielded added evidence for the need to monitor for spans longer than 24 hours. The extent of day-to-day variability can be so large for some individuals that a diagnosis based on a single 24-hour span can be very misleading. At a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation) in Brussels, Belgium, on March 17-18,1995, a resolution was reached that recommended monitoring for 7 days at the outset [77]. Not only does the circadian assessment become more reliable, a glimpse if not insight into the about-weekly (circaseptan) component is also obtained. Circaseptans were found to be particularly prominent in early extrauterine life [78] and to regain prominence in the elderly [79], while persisting in isolation from society [80, 81].

Instead of being discarded, the data are saved for as-one-goes analyses in a form compacted into characteristics of the rhythms with the next higher frequency, resolved by repeated passes directly from the original data, as long as data storage permits it, or from the computed endpoints of chronome elements such as rhythm characteristics of already-resolved higher frequency components, when compacting becomes indispensable [78, 80]. The "recycling" by these repeated passes of accumulating BP and HR data led to the identification of new disease risks, such as CHAT, CAHRVs (chronome alterations of heart rate variability - e.g., a decreased heart rate variability, along the circadian scale), and an excessive pulse pressure. These conditions relate to altered variability within the physiological range, which, once recognized, can prompt the institution of preventive measures.

Retrospective analyses confirmed the results by showing that an excessive circadian BP amplitude is associated with an elevated left ventricular mass index, determined on all subjects, and used as a surrogate outcome measure [82-84].

K. Otsuka [85] has reported that among the risks assessed concomitantly, CHAT was found to represent the largest (720%) increase in the risk of cerebral ischemic events, compared with 310%, 370%, 160%, 170% and 150% in relation to MESOR-hypertension, old age, a positive family history of high BP and/or related vascular disease, smoking and alcohol consumption, respectively. A reduced 24-hour standard deviation of HR (DHRV) was also associated with an increased risk of vascular morbidity, coronary artery disease and cerebral ischemic events in particular. In both cases, the endpoint exhibits a nonlinear relation with vascular disease risk [86].

The lack of a statistically significant correlation between the circadian BP amplitude and the 24-hour standard deviation of HR suggested that CHAT and DHRV constitute separate disease risks. The likelihood of a morbid event is about doubled when both conditions are present than when either diagnosis is present alone [87]. EPP is also mostly a risk factor separate from CHAT and/or DHRV (Table 3). The relative risk of a morbid event is calculated by comparing patients who had one or several chronome alterations with patients who had acceptable dynamics (circadian BP amplitude, 24-hour standard deviation of HR, and pulse pressure).

TABLE 3: Relative risk of morbidity associated with DBP-CHAT and DHRV, singly or in combination*

	Group		
	DBP-CHAT-only	DHRV-only	DBP-CHAT and DHRV
N of patients	20	19	5
All morbid events	4,43 2,13-9,19	5,33 2,71 – 10,46	10,12 5,51 – 18,58
Cerebral ischemic events	9,49 [2,28 – 39,49]	13,32 [3,61- 9,11]	37,95** [11,35- 126,9]
Coronary artery disease	3,16 [0,72-13,91]	8,32 [3,01 – 2,97]	6.32 [0,96-41,49]
Nephropathy	6,32 [2,08 – 19,20]	4,99 [1,44- 17,30]	18,97** [7,06 – 50,99]
Retinopathy	2,11 [0,51 – 8,78]	1,11 [0,15 – 8,09]	4.22 [0,67 – 26,50]

*RR listed with 95% confidence interval;
DBP: diastolic blood pressure;

CHAT: circadian hyper-amplitude-tension;
DHRV: decreased heart rate variability.
Total number of patients: 297.
**RR associated with combined DBP-CHAT and DHRV is statistically significantly larger than RR associated with either DBP-CHAT or DHRV alone.

To detect CHAT, and for other diagnostic and therapeutic reasons, Franz has advocated that single measurements should be replaced by an around-the-clock profile, for a week or longer if need be, at the outset, to be obtained preferably by ambulatory monitoring. Indeed, several studies comparing the diagnosis reached on the basis of ambulatory monitoring (for 7 days) versus single measurements taken in the physician's office, reached the conclusion that an error of about 40% may be associated with the current approach. Two culprits were identified, namely:

1. The reliance on single time-unspecified measurements, based on the mistaken assumption that a procedure used on thousands of people in large clinical trials can readily be transferred, without qualification, for a decision to be made for the individual patient. Even the most accurate measurement taken in the clinic, usually associated with an error of less than 5 mm Hg, needs to be interpreted in the light of a within-hour standard deviation of BP of the order of 7 mm Hg and a within-day change often exceeding 50 mm Hg; even a 24-hour profile obtained by ambulatory monitoring is no gold standard in view of the large

day-to-day changes in circadian characteristics [75, 76]; and

2. The anachronism of interpreting measurements of a variable known to undergo a prominent circadian rhythm in the light of fixed limits, irrespective of time, age, or gender.

From a purely theoretical viewpoint, a sizeable number of patients with a circadian amplitude close to the upper limit of acceptability and a commonly found acrophase in mid-afternoon, is likely to be diagnosed as normotensive in the morning but as hypertensive in the afternoon [88]. This situation was actually encountered in practice, as described in print in detail by Frederic C. Bartter [89], prompting him to emphasize the indispensability of the cosinor in routine practice.

Chronobiological research shows that long-acting carteolol had been shown earlier to depress the circadian and circaseptan amplitudes of blood pressure and is therefore a candidate drug for the treatment of circadian overswinging or circadian hyper-amplitude-tension.

Table 4 shows that, in a woman with CHAT (YA), long-acting carteolol can also reduce the circannual amplitude of SBP and DBP and, at one of the two test times (in measurements taken at the time of getting up), the amplitude of heart rate. We document that the detection of the effect upon the amplitude of HR is circadian stage-dependent.

TABLE 4: Long-acting 15 mg/07:30 carteolol lowers MESOR and double circannual amplitude (2A) of systolic (S) and diastolic (D) blood pressure (BP) consistently in measurements at awakening (top) or at bedtime (bottom) with a possibly undesirable effect on heart rate, seen only at awakening, with the serious qualification of aliasing.

Parameter	SBP (mm Hg)	DBP (mm Hg)	HR (beats/min)
	P		
	Data at getting up		
1	3	<0.001	
	Data at bedtime		
	<0.001		
	0.800		

*Assessed in an adult woman, YA, treated for the first ~30 months and not treated for the ensuing ~60 months, in self-measurements on awakening (top half) and at bedtime (bottom half). P-values from comparisons of circannual rhythm parameters subject to qualification of *ante hoc ergo propter hoc,* or rather of *ante cum hoc, post sine hoc, ergo propter hoc,* where *hoc* applies to *medicina, therapia et ceteris.* This qualification applies to each "washout" study of drug effects with the washout necessarily long in the case of beta-blockers.

**360˚ 1 year; 0˚=January 1 of year preceding data collection.

The damping examined by spectra (not shown) involves not only the circannual but also transannual amplitudes as novel chronopharmacodynamic actions; it awaits testing whether such an effect is useful for patients with CHAT with or without an excessive about-yearly and transyearly blood pressure swing, who have no deficient or marginally lowered circadian heart rate variability, that would be a contraindication.

A public service task of physiological monitoring should indeed be within the mandate of those not only in local, but also in federal government agencies dispensing resources, and it is just a first step toward education in a much broader chronobiologic literacy [90].

R.M. Zaslavskaya [91, 92] noted that melatonin can lower blood pressure in patients resistant to conventional antihypertensive therapy. She has now extended her findings to patients with other problems involving the circulation, including patients with heart failure and angina. Reportedly, her patients derived therapeutic benefit from melatonin as it lowered the number of anginal attacks and the number of occasions when nitroglycerine was used, and improved the ECG. An association between melatonin and the blood circulation was noted earlier by Lennart Wetterberg in an international broader-than the Japanese/USA study of various endocrine indicators of disease risks [93].

Taking a 24-hour ambulatory profile is still a spotcheck; from the viewpoint of a 24-hour rhythm it is equivalent to taking an ECG for one cardiac cycle, perhaps one second. A still greater limitation applies to the assessment from 7-day records of a circaseptan rhythm, since in human adults the circaseptan amplitude is much smaller than the circadian. For diagnosis and therapy, we need series of a length that allows the assessment of infradians that can modulate circadians, the more so now that drugs for individualized treatment have been developed and become availa ble. Individualized chronotherapy can be based on different drugs, whether we wish to lower an excessive amplitude of blood pressure or raise the variability of heart rate, when it is too low, as discussed elsewhere.

Chronotherapy is being considered as an adjunct to treatment of other disorders. It has become evident that all living things need a certain period of darkness and then quality daylight in order to function properly. Understanding and control of circadian rhythm is a very powerful tool in modifying human health.

In the subsequent chapters the questions of astrochronobiology interaction will be considered.

CHRONOASTROBIOLOGY

The physical environment of life is characterized by several major periodicities that derive from the motions of the earth and the moon relative to the sun. From its origin some billions of years ago, life has had to cope with pronounced daily and annual cycles of light and temperature. Tidal cycles challenged life as soon as the edge of the sea was invaded; and on land, humidity and other daily cycles were added to the older challenges of light and temperature. These physical periodicities clearly raise challenges – caricatured by the hostility of deserts by day and of high latitudes in winter – that natural selection has had to cope with; on the other hand, the unique stability of these cycles based on celestial mechanics presents a clear opportunity for selection: their predictability makes anticipatory programming a viable strategy.

Many scientists have studied mutual relation of alive organism with its environment, that preceded modern understanding of the biosphere. J.B. Lamark in the book "Hydrogeology" has devoted the whole chapter the influence of alive organisms on the terrestrial globe. He wrote: "... In nature there is a special force, powerful and constantly working, which has ability to form combinations, to multiply them, diversity them... The influence of alive organisms on substances of the earth surface that form its external crust is rather considerable, because these substances are indefinitely various and numerous, they are constantly changing covering by their gradually collecting and the time remnants all terrestrial globe".

V.I. Vernadsky (1926) considers biosphere as area of life, which basis - interaction of alive and born substance, he wrote: " Alive organisms are perform biosphere function connected they huge with it geological force, determining it".

During evolutionary development the man was exposed to the whole complex of ecological influences in the process his settlement on the Earth. The factors of external environment constantly influencing organism, aspire to change its condition, but thus the specific and not specific mechanisms preventing or compensating arisen changes are included. For maintenance of normal ability to live in the appropriate living conditions physiological and morphological norms are formed, which are the special form of the organism adaptation to the environment.

The organism adaptation to constantly varying conditions of external environment requires a wide range of functionalities and fast switching of major physiological systems to a new mode of ability to live.

The individual temporary scale lays in the basis of complex functional system of the organism. In new natural conditions organism is quite often the influence of the unusual, excessive and rigid environment factors inadequate to its nature. Now traditional ways of adaptation vary especialy in connection specific and most complex social-biological adaptation at the level of system "society-nature". Thus the interrelation of the man's mechanisms adaptation to various conditions is shown depending on individual organism properties, such as its chronoresistation, and also ethnoconstitution perfomans [43].

Studying alive organisms, the researchers always remember about closest connection with the environment. I.M. Sechenov, as is known, believed, that concept organism inevitably includes also the environment where its lives. This ideology was basis for the ecology, the ecological physiology, antropoecology and astrochronobiology. So, organism and environment are inseparable.

The term «chronoastrobiology» is derived from «chronome» (time structure) and «astrobiology» (reciprocal implications of biology and space studies).

Chronoastrobiology extends to a concern for life's origins and to broader, including physical aspects of eras before our own and their evolutionary effects on the temporal organization of psycho-physiological functions in today's living organisms.

To be sure, the discipline seeks practical as well as basic knowledge. It strives to optimize psychophysiology for life on earth and elsewhere, with focus on disease prevention, or 'prehabilitation', as well as rehabilitation. It is sensitive to the challenges of extraterrestrial colonization and to the fact that maintaining good health in space in the absence of hospitals may require special understanding of the interactions between human physiology and cosmic forces that occur largely in an otherwise neglected so-called normal range.

Biologists need the caution of physicists who had found the quasi-persistence of oscillations with a period somewhat longer than a year in magnetism, including aurorae and cosmic rays [94-98] and who, like H. Schwabe [99, 100] were unsure of the stability or persistence of the periods they resolved and so stated. In 1968, Ralph Shapiro marked his spectrum of the international magnetic character figure C_4 by peaks at 1.41 and 1.10 years in a time series covering the span from 1884 to 1964. Shapiro also deserves credit for testing the statistical significance of the peak and for reaching the 5% level with one approach. Fraser-Smith confirmed this in 1972: he found that [94]:

There was some indication of a 1.4-year line in the (*Ap*) spectrum of Fig. 7, and it is a more obvious feature in the spectrum for the daily *Ap* data. An unexpected line occurs at a period of 1.09 years, with an amplitude not much smaller than that of the 1.43-year line. These two lines are all that are evident with periods greater than 6 months. Again, there is no trace of an annual line. (Indeed, there was, and is, no such line in the spectrum of the geomagnetic index aa in the data reported by Bartels in 1932 after folding [96]. Folding is fine for visualizing the circasemiannual component, but must not be used to describe non-existent yearly variation in the antipodal aa index in toto, Fig. 7.)

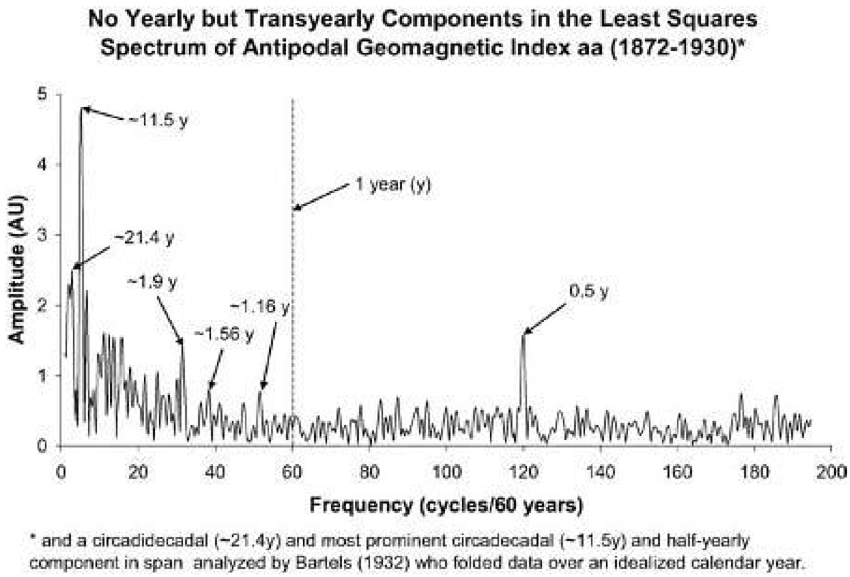


Fig. 7. Our meta-spectral analysis of data on a geomagnetic index published after folding in 1932 as "variations annuelles" shows a valley, not a peak, in a spectrum [97], a fact commented upon explicitly as the lack of an annual component in [94]; a valley is seen in the spectrum in [97].

In any event, by 1972 both a near-and a far-transyear were clearly noted by two independent investigators [94, 95], but there was no component with a corresponding period in sunspots. In the discussion [94], Fraser-Smith observed: The *Ap* spectrum also has weak lines at periods of 1.43 and 1.09 years that may not be related to anything connected with the sun. (There are no lines in the sunspot spectrum at either period.)

In the era before satellites had provided sufficient data on the particles streaming by them (dubbed the solar wind since they reportedly stem largely from the sun), one could rely only on Wolf's relative sunspot numbers. (But with solar wind data and biological counterparts available, reciprocal periods came to the fore, such as new lessons in Fig. 9.)

To complete the story of the discovery of transyears in geophysics, Samuel M. Silverman and Ralph Shapiro in 1984 [98] examined Swedish auroral sightings for the span from 1721 to 1943: "an unexpected peak near 1.4 years is found … [it is] statistically significant at between the 5% and 1% level and found consistently in a sequence of spectra covering consecutive, overlapping, approximately 22-year data segments … The 1.4-year peak shows a strong modulation of about 65 to 68 years … The origin of this peak is unknown." Richardson cites some of these earlier papers when he reports on an oscillation of 1.3 years in the solar wind [101]; a moving spectrum suggests, in the hands of others [102] and our own [103, 104], that in all these cases we are dealing with very wobbly spectral components. This wobbliness, documented in physics and in biology, can be checked for geomagnetics for a century and a half or so, and in organisms probably for much longer. Here, the two disciplines can communicate and support each other.

Biomedicine can serve physics, since organisms are almost certainly older than the oldest instruments of physicists even if we accept the report that the Chinese used magnets thousands of years ago. Organisms before and after hominization have coded at least some environmental periods in their genes [105,106]. The periods in biology may not all be the same as those reported in physics, but Fig. 8 suggests that similarities

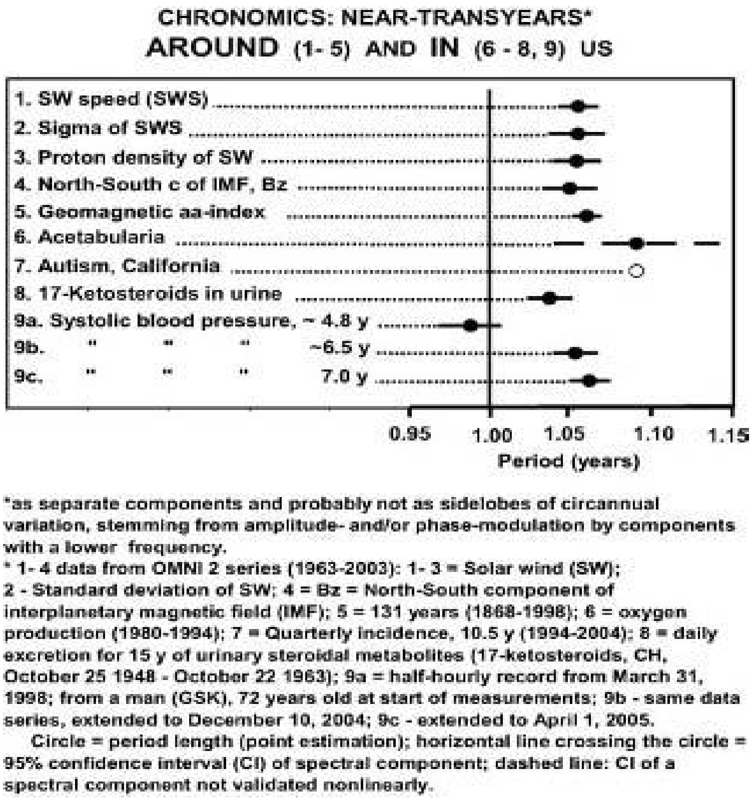


Fig. 8. Transdisciplinary near-transyears in solar and terrestrial biophysics and biology.

exist between the near-transyear, the hourly excretion of steroids and that in 131 years of aa and in other series of geomagnetics or aurorae [94–97]. The biological and physical components in Fig. 8 all allow the rejection of the zero-amplitude assumption by linear–non-linear spectral analyses. The similarity of τs is not limited only to a geomagnetic index such as aa or Ap [94, 97]. It gains in importance if a similar near-transyear is also found in the changes of the speed of the solar wind and in the standard deviation of these changes in SW speed, and further in the solar wind's proton density, Fig. 8. It is also interesting that longer periods corresponding roughly to the 1.44 or 1.47 years [95,97,98, 107], as in geomagnetics, are also found in the temperature of the solar wind.

Chronoastrobiology and its parents, chronobiology and chronomics, are here to stay; they might produce an understanding of where we came from, of what we can now do for prehabilitation to forestall the need for rehabilitation, and of how we can thus get safely to where we wish to go in space. This challenge has been under-appreciated in the US by contrast to endeavors abroad.

The findings in hand underscore the need to improve a bioscience and health care system based on evaluating data from spot-checks by eyeballing. The alternative is a time series-based, computer-analyzed time structure unfolding and quantifying everyday physiology, rather than leaving it obscured by the misleading notion of a homeostatic ther-mostat-like set-point in the fiction of an unresolvable 'normal' range of variation.

Focus upon the detection and treatment of risk elevation related to magnetic fluctuations is particularly needed for travel in extraterrestrial space; it also promises immediate spinoffs for people living on the earth's surface, generally from cost-effective prehabilitation to replace rehabilitation as soon and as far as possible.

Exogenous rhythms: only conditioned reflexes?

Early in the 20th century, Ivan Petrovich Pavlov (1849–1936), for generations Russia's most celebrated bioscientist, was alert to record the time of day at each step of some of the now-classic studies in Russian and world science. Pavlov's conditioned reflex paradigm was misused by the Stalinist regime's Lysenkoism to suppress other science. Yet on both sides of the iron curtain, conditioned reflexes were usually invoked to account for biological rhythms in classical physiology and psychology – in the West up to 1949 [108] and in the East [1109] for much longer.

Eventually the conditioned reflex model "impressed from without and persisting from within" [108] was replaced by an appreciation for built-in endogenous rhythmicity, at first for circadians when it became clear by 1950 that circadian rhythms were inborn in inbred strains of mice [41]. These are more than a phenomenon reacquired by each individual, whether reflexive, imprinted or 'learned'. Lighting and other environmental cycles rather than generating periodicity de novo synchronize the organism's endogenous rhythms (such as in newborn human infants) with daily activity and nightly quiet [108]. Thus in human twins as well [41] as in earlier forms of life such as unicells and bacteria [41,110], the about 24-hour circadian cycle was found to have been genetically coded.

Exogenous rhythms: a heliobiological echo without explicit evolutionary aspects

Pioneering Russian chronobiologists went far beyond circadians to focus on circadecadal (about-ten year) changes, and they deserve to be widely known beyond their homeland where they were revered: Alexander Leonidovich Chizhevsky found an about 10-year cycle in 100 years of statistics on the incidence of cholera and described life on earth as "an echo of the sun". A.L.Chizhevsky was deservedly offered a Nobel Prize in 1939 but was forced to turn it down by the Stalinist government, and was even imprisoned from 1942 to 1958 [111-113].

Nikolai Dmitrievich Kondratiev, the founder of the Moscow Conjuncture Institute, detected economic cycles of about 50 years [114]. «N.D. Kondratiev organized (the Conjuncture Institute) in October 1920, at a time when the creation of centers for business cycle analysis was an international phenomenon» (albeit without estimates of the uncertainty of the cycles'characteristics). A group of economists associated with Kondratiev proposed, as an alternative to Stalin's forced industrialization policy, a market-led program … Kondratiev … hoped that the Conjuncture Institute would demonstrate to the (Stalinist) leadership the inadequacy of their understanding of the Soviet economy. Instead, the institute was closed permanently in 1930, when he was arrested. In September 1938, he was sentenced to death" [116].

Partly built-in non-photic cycles?

Recently are discussed the question of whether we resonate (only) concurrently in response to subtle factors that prevail at a given time (exogenous rhythm) [116–123], as Frank A. Brown Jr put it originally, but not subsequently, when he coined the term ‘autophasing’ [124]; or again as an immediate physiological ‘reverberation’ to exogenous factors, i.e. as a mere echo of our sun and of the cycles in our cosmos, as A.L. Chizhevsky put it earlier [111– 1113, 125]; or as reactive and, to that extent, exogenous periodicities, as G. Hildebrandt put it originally, but not later [126]. In all of these instances, the very early champions of the exogenicity of circadian rhythms switched to the acceptance of some degree of endogenicity. While citing the foregoing ‘phrases’ used by important pioneers in the field, we wish to qualify their stand and ours [41] by adding that almost certainly all scholars in the field increasingly realized that organisms are open systems, and that the debate on exogenous vs endogenous is primarily one of emphasis on the relative importance of one or the other aspect and approach.

The historical plea to recognize the extent of endogenicity (for a review, see [41]) is in keeping with the now general recognition of some built-in part played by the organism with respect to circadians. Evidence is accumulating to consider more than a concurrent or slightly delayed echo (physiological reverberation?) for rhythms other than circadian as well [127]. There is a spectrum of coded built-in cycles with components in us that were heretofore unknown or not mentioned in physiology textbooks; their periods near-match cycles around us ([128]; cf. [41, 122, 123]); they become manifest after exposure to single stimuli, which carry no information as to period, as documented best for circaseptans [90, 128].

Exophased endocycling

In a model of exophased endocycling, the phase is exogenous and the period partly endogenous, in keeping with a demonstrated 'free-run' of endogenous circadians and circaseptans. For these rhythms, many replications of a cycle can be more readily tested than in the case of yet longer cycles. For the cycles with long periods, the nonoverlapping 95% confidence intervals (CIs) for near-matching external and internal cycles (with a length of, e.g. years or decades) strongly suggests some degree of endogenicity [129]. The use of exophased endocycling emphasizes by 'exophasing' rather than 'autophasing', that a number of rhythms appear to be 'induced' by a single stimulus, which has led to calling them 'exogenous'. But the fact that a single stimulus carries no information about any period is a hint of endogenicity. This line of evidence, along with free-running, was emphasized by others in the early days of circadians [41] and by us for circaseptans and other non-photic cycles that act as triggers.

A kidney transplant is followed by rejection episodes at about 7-day intervals, as removal of a kidney induces a wave of

DNA-labelling and mitotic peaks at 7-day intervals. Human birth is associated with many amplified population cycles such as the biological near-week, month, half-year, transyear and decade, presumably all coded by natural selection as cycles of non-photic origin. The use of endocycling thus refers to the particular cycle length as a built-in feature, yet it is also eminently suited for resonance. Endocycling complementing exophasing, i.e., internal mechanisms contributing to a cycle's length, are not always stated but probably implied in the short phrases cited by pioneers who originally assumed that even circadians were purely reactive, as in the case of Frank Brown before he coined the term ‘autophasing’.

Non-photic/photic amplitude ratios

Further evidence of endogenous chronomic components stems from the shift in the course of ontogeny [128] and phylogeny [90] of the ratio of the amplitudes (A) of the biological signatures of certain non-photic cycles vs the signature of the photic cycle with the nearest period length. Illustrative amplitude ratios are the A of the week vs that of the day or the As of the transyear (e.g. of ~1.3 years) or of the ~10.5 or ~21-year vs the A at the calendar year [130]. The genetic coding in life of photic cycles such as the alternation of day with night is more prominent in *Escherichia coli* and in cyanobacteria than the coding of a near-week or circaseptan component, which is not detected in air bacteria and staphylococci [41, 110].

By contrast, there is a transient prominence early in ontogeny of the biological near-week over the circadian rhythms in certain variables of a unicell [41], crayfish [131], rat [132], pig [133] and human baby [41]. Some relatively early forms of life such as *Acetabularia* have coded non-photic unseen cycles around us, and traces of this coding appear early and consistently in the ontogeny of non-human animals and of human newborns. These non-photic schedules may have been the major ones that life was exposed to at the bottom of the sea or in the interior of the earth with no known cycles of light and darkness, or in some other cosmic location in the possible event of panspermia. This theory holds that reproductive bodies exist throughout the universe and develop wherever the environment is favorable. Hence, the proposition that life could have come from other entities in the universe cannot be ruled out. We can assume, however, that life may have developed before photosensitive pigments did, and it certainly came about before eyes developed.

Biological mimicry of longer than yearly oscillations found in satellite data

In 1994, John D. Richardson, at the Massachusetts Institute of Technology in Cambridge, USA, found oscillations with a period of about 1.3 years in the changing speed of the solar wind, i.e. the particles ejected into space by the sun [134]. In 2000, Kalevi Mursula and Bertalan Zieger further reported a change in the same speed measurements, as a function of Schwabe's circadecadal cycle in sunspots from about 1.3 to 1.6 years [135]. By now, a longer series has become available as Omni2 (http: //nssdc.gsfc.nasa.gov/omniweb/ow.html) which combines data from several satellites, displayed in both the time (Fig. 9a) and frequency (Figs 9b and 9c) domains.

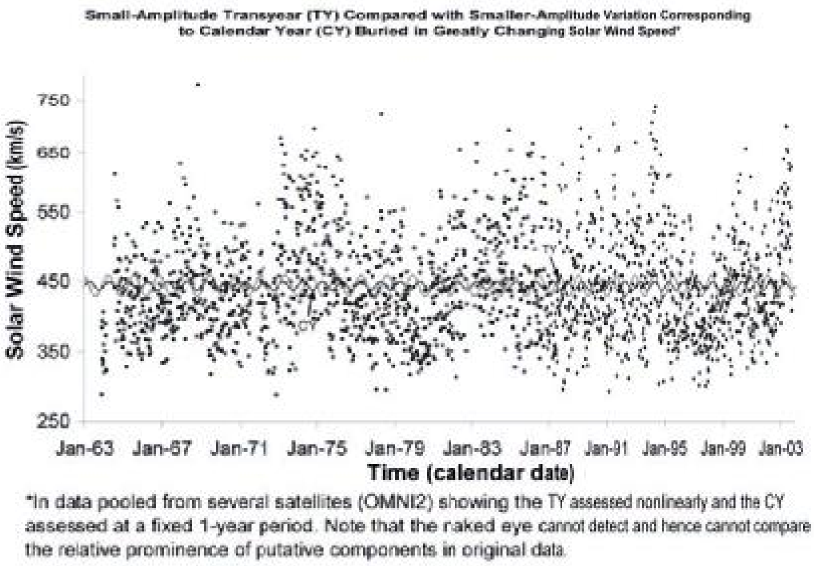


Fig. 9a. A composite series of solar wind speed shows a great dispersion of values confounded by pooling data obtained by different satellites at different times.

Time-macroscopically, with the unaided eye, without an analysis in Fig. 8b, any regularity in the variation could not be quantified or recognized. Time-microscopically, we show a cosine curve with a period detected by the spectral analysis and another curve (with a smaller amplitude) with a cycle length corresponding to the calendar year. The yearly oscillation (with the smaller amplitude) is seen to start roughly in phase and then get out of and back into phase, with the oscillation with the larger amplitude (the transyear).

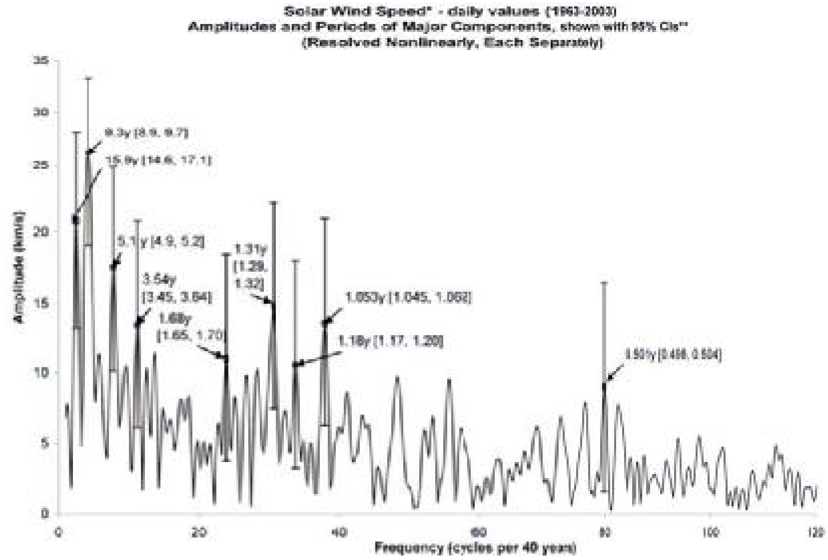


Fig. 9b. Orienting periodogram showing several transyears, including a 1.68-year, corresponding roughly to one reported by Mursula and Zieger [135], in addition to Richardson's ~1.3-year oscillations [134]. The several separate components with periods slightly longer than 1 year have 95% confidence intervals overlapping neither one another nor the precise 1.0-year when they are computed one at a time by linear–nonlinear least squares from the data of Fig. 9a.

The naked eye would miss these oscillations without a model like that included in Fig. 9c. We must rely on the periods given with an approximation of their uncertainties in parentheses as 95% CIs in the detailed Fig. 9c, in which all candidate components are fitted and resolved concomitantly. That the 0,5 year component constitutes an artifact from unequally spaced data on the solar wind is a possibility. That a 1.7-year component previously reported [135] (albeit lost in a concomitant resolution in Figure 9c) is real can be assumed since it is genetically preserved in its biological near-matches in unicells and humans.

A peak in the 'periodogram' of Fig. 8c reveals a component with an about 1.3-year period, as well as an ~1.054-year periodicity, each with a 95% CI that does not overlap the precise calendar year. Gliding spectral windows are shown in Fig. 9d, with time on the abscissa and frequency on the ordinate; the amplitude (in the top half of the display) and percentage rhythm (in the bottom half) are represented by different shading; they show as contour maps during the 1970s, first a component with a period of 1.3 years which gradually lengthens until it is of about 1.6-year length before 1978. Thereafter, this component disappears, to reappear only before the end of the millennium. Still in the early 1970s, there is also a component of about 1.0-year length. A very prominent 1.3-year is apparent only in the late 1980s and early 1990s. The transyearly components in the global spectral windows of Figs 9b and 9c are indeed wobbly components and not spectral lines or even consistent bands.

Solar wind data have been recorded only during the past several decades. Hence, it seemed worthwhile in Figs 9e and 9f to gauge another kind of solar activity during a different prior timespan, as the Wolf numbers after filtering shows that for spans of 60 years a transyear can be present after it had been undetected (with the resolution used) for even longer time spans. Geomagnetic indices are a much better proxy for solar activity and Kp has been used for this purpose [135].

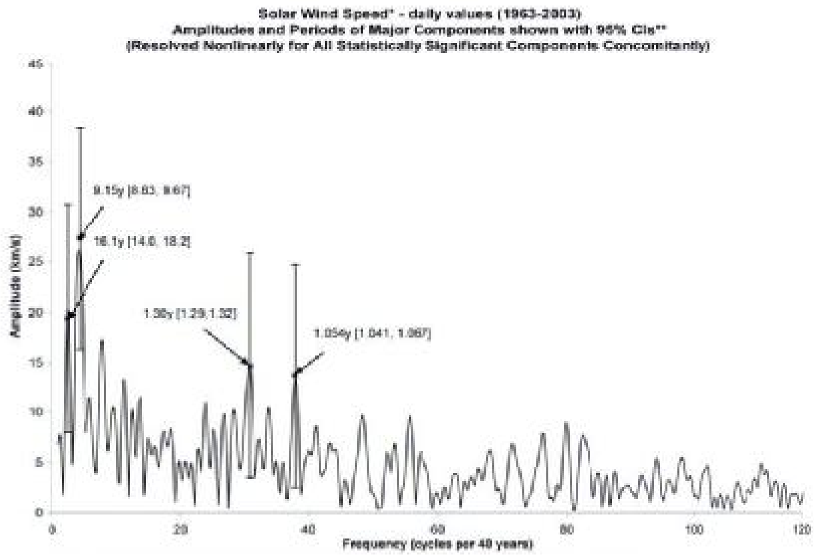


Fig. 9c. Periodogram of components resolvable concomitantly, showing, as did Fig. 8b, no component with a 95% confidence interval overlapping the precise 1-year length, as also happens to be the case in Fig. 10a for a 15-year series consisting of the daily excretion of important hormonal metabolites. Without implying any causal connections, it seems important to note that asynchronized near-yearly components can characterize both physical environmental and biological variables.

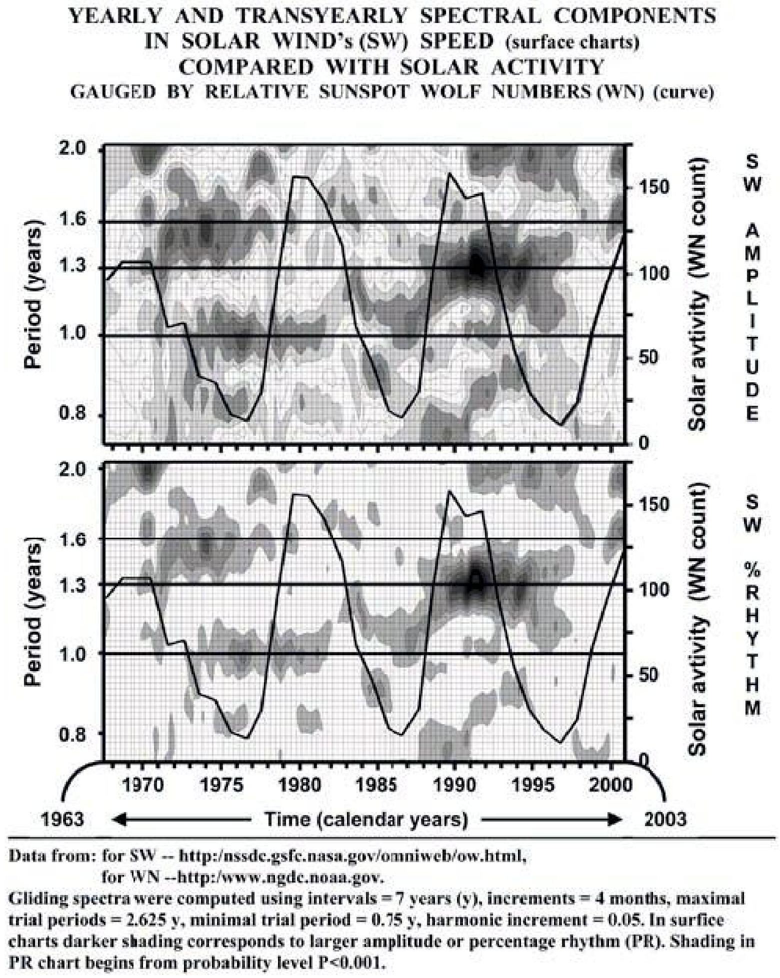


Fig. 9d. Gliding spectral windows of amplitude (top) and percentage rhythm (bottom) show the alternation of an ~1.6-year and an ~1.0-year component on the one hand with a 1.3-year component, but not with alternating solar cycle numbers, quoted by Mursula and Zieger [135].

Any artifactual damping possibly resulting from combining solar wind speed data from different satellites remains unevaluated. These and other qualifications not with standing, it is noteworthy that in life on earth a relatively very small change outside us in the solar wind, unseen except for aurorae, can be prominent at certain ages [129].

To many biological time series, the qualification of artifacts from combining time series from different satellites in different locations does not apply. The dynamically changing patterns of some physical variables such as solar wind speed (Fig. 8d) and Wolf's relative sunspot numbers (Fig. 9e and 9f) qualify the wobbly nature of the unseen transyears around us. With this qualification, in any time series, we define a transyear as a spectral component resolved with a 95% CI between 1 and 2 years, overlapping neither of these lengths of time. Such a component of biological time series – a mimicry in length of the changes in the speed of the solar wind – can override in us the effect of the seasons at middle latitudes [129, 130, 136-139].

A highly pronounced spectral component in WN (Fig. 9e) has a τ of about a decade, and strong components with τs of several decades are also present in the WN spectrum, visible to the naked eye. Against this background, tiny oscillations (if they exist) cannot be distinguished. GK is tempted to use the analogy of a candle flame that cannot be seen when it is illuminated by a strong beam of light from another source. If that source is switched off, the candle's light becomes visible. Filtering is a mathematical procedure for 'switching off' powerful oscillations. Many filtering procedures exist. One of the simplest is the application to an original data series of a moving third-order

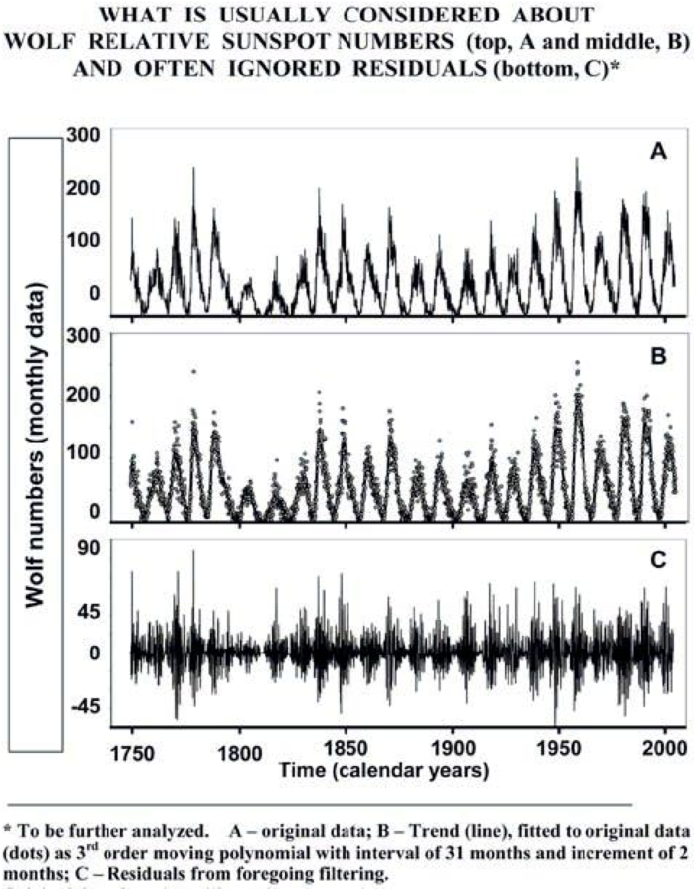


Fig. 9e. To examine the behavior of solar activity for a much longer span, covering centuries as compared to the several decades for which satellite-made solar wind speed measurements are available, Wolf's relative sunspot numbers were filtered to uncover any components in a spectral window of period lengths (τ) between 2 and 0.5 years. Daily data of WN values during ~2.5 centuries (1750–2004) were obtained from http://ftp.ngdc.noaa.gov/.

polynomial with a window length (interval, I) equal to any τ value. Such a window can be shifted along the data series with any shift value (Sh=increment). As a result, the series will be divided into two new series. The first of these secondary series contains oscillations with τ>I (trend) and the second with τ< I (residuals). The data from section A were filtered by mowing a third-order polynomial with I=31 months (2.625 yr) and Sh=2 months. The trend and residuals are shown in section B, only the residuals in section C.

A global spectral window of WN residuals (Fig. 9f) is shown on the right, with peaks corresponding to bands around 1–1,3 yr and around 0,8–0,6 yr. These bands are not sharp, suggesting that the spectral components are not stable (non-stationary). A gliding spectral window confirms this hypothesis and is plotted as a contour map (surface chart prepared with Microsoft Excel software). There is no obvious consistent variation as a function of time in the gliding spectral window (left) of components seen in a global spectral window (right). A 1.3-year component, as shown in black shading, is prominent at one time, less prominent in gray at other times, or may not be resolved at still other times. Differences in prominence with shading coming and going are also seen around the trial period of 1 year rather than at precisely 1 year. Thus, among many other components, all transient with the resolution used, we find that the sunspots, like the solar wind and geomagnetism, have some near-years that are not exactly yearly, and also have some components of about 1.3-years, all time-varying if not transient. After a period of ~1.3 to 1.6 year length was found in satellite-collected data on the changing speed of the ionized gases ejected by the sun into interplanetary space, i.e., in the solar wind, periodic components of similar length are also found in biospheric data. These include a 15-year series of daily urinary 17-ketosteroid (17KS) excretion a clinically healthy man (Tables 5 and 6).

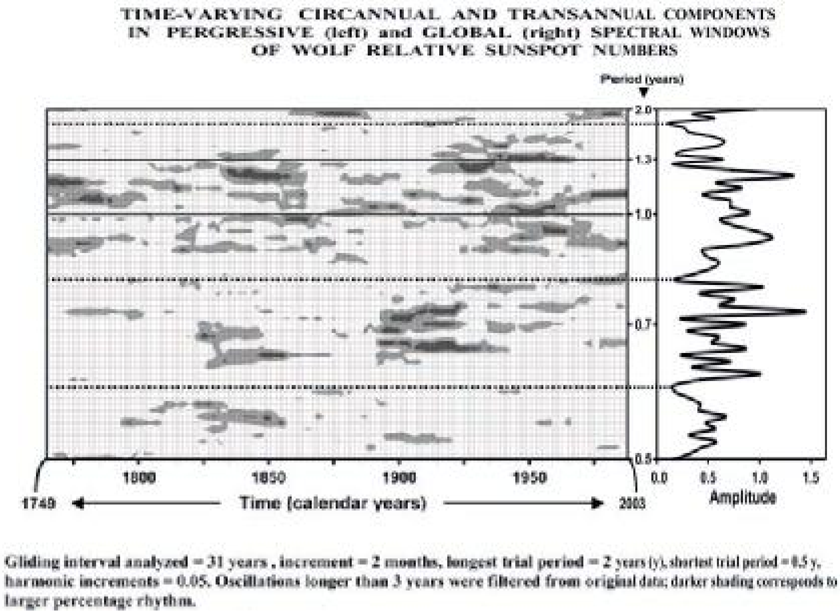


Fig. 9f. A least squares periodogram with trial periods between 2,0 and 0,5 years was computed with harmonic increments=0,05. For approximations at every trial period, several statistical parameters were estimated, including the coefficient of determination (i.e. the percentage rhythm).

Moreover, as in the half-hourly blood pressure measurements over 6 years of another man, the 95% confidence intervals (CIs) of the transyear found in the 17KS do not overlap the CIs of variables related to the near-matching components in the solar wind. These findings are in keeping with the assumption that the non-photic transyear may have been built into our evolving genome, as in the case of the circadian rhythm related to the much more prominent photic and thermic environmental day.

TABLE 5: Transdisciplinary imaging in time of a series of daily human 17-ketosteroid (17KS) excretions*

	Transyear (TY)		Near-year (NY)		Year (Y)
Data series (units)	Period (years)	Amplitude	Period (years)	Amplitude	Amplitude
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)
17-KS (daily) (mg/24 h)	1.313 (1.289,1.338)	0.23 (0.16,0.31)	1.036 (1.023,1.049)	0.26 (0.18, 0.34)	0.19 (0.12,0.26)
Urine volume (daily) (ml)	1.392 (1.352,1.432)	36.82 (18.20, 55.43)	1.000 (0.987,1.013)	60.14 (41.73, 78.55)	60.14 (43.44, 76.83
K_p (daily) (AU)	1.301 (1.235,1.367)	0.07 (0.00,0.14)	1.056 (1.036,1.077)	0.15 (0.08, 0.22)	0.05 (—,—)
Wolf N (daily) (AU)	1.262 (1.233,1.291)	8.53 (4.38,12.67)	1.049 (1.017,1.080)	5.40 (1.21, 9.58)	2.97 (—,—)
K_p (matching dates) (AU)	1.224 (1.163,1.284)	0.09 (0.00,0.18)	1.052 (1.018,1.085)	0.12 (0.04, 0.21)	0.07 (—,—)
Wolf N (matching dates) (AU)	1.388 (1.316, 1.461)	5.62 (0.46,10.78)	1.000 (0.965,1.035)	6.05 (0.90, 11.20)	6.05 (1.38,10.72)

*Covering (with gaps) 15 years; N data: 3719; N days: 5476; AU: arbitrary units; underlining emphasizes non-overlapping 95% confidence intervals (CIs). Note further by * non-overlap by CIs of near-year of precise year period.

When the solar wind data obtained from satellites that now cover several decades are aligned with biological data we learn that the human transyear may be genetically coded. One line of evidence stems from non-overlapping 95% CIs of nearmat-ching periods in and around us, a criterion that had earlier led to the recognition of the built-in nature of circadians [41]. The precedent of the biological week as a counterpart of a weak near-weekly component in terrestrial magnetism, found by biologists [128], originally led to the proposition of reciprocal natural environmental and biological periods [128].

Table 6: Ratios of the amplitudes of the transyear vs. near-year (A_{TY}/A_{NY}) and of the transyear vs. the precise year (A_{TY}/A_{Y})*

Data series (units)	A_{TY}/A_{NY}	A_{TY}/A_{Y}
17-KS (daily) (mg/24 h)	88.5	121.1
Urine volume (daily) (ml)	61.2	61.2
K_p (daily) (AU)	46.7	140.0
Wolf N (daily) (AU)	158.0	287.2
K_p (matching dates) (AU)	75.0	128.6
Wolf N (matching dates) (AU)	92.9	92.9

*Covering (with gaps) 15 years; N data: 3719; N days: 5476; AU: arbitrary units; underlining emphasizes non-overlapping 95% confidence intervals (CIs). Note further by * non-overlap by CIs of near-year of precise year period.

That natural cycles in magnetism [128] have human-made socio-techno-environmental counterparts is now documented for the case of the week [94], confirmed [104] and recognized as a putative gauge of global magnetic pollution [141]. That circadians have entered our genes early in phylogeny, even at the stage of bacterial evolution, is now amply recognized, after having been disputed for decades by opinion leaders in the field who depended on eye-balling of data and classical rather than time series statistics [41,110, 142-145]. If non-photic cycles are also coded in genomes, this would be much more than a mere echo of solar events. The next task is to explore the genetics of these non-photic periodicities at the molecular level; this is, of course, most readily considered in the homeland of Chizhevsky and of V.I. Vernadsky [146].

The biological about 1.3-year changes have been recorded only for the past few decades, while there are satellites to carry instruments for measurements of changes in the speed of the solar wind. We may try to reconstruct how the solar wind behaved in the remote past by comparing in phylogeny, starting relatively early in prokaryotes such as air bacteria and staphylococci [130] and early in human ontogeny, the relative prominence of non-photic vs. photic spectral components.

For certain variables and at certain ages, a transyear (e.g. an about 1.3-year) can be more prominent than the yearly change from summer to winter. This is found for oxygen evolution in *Acetabularia*, in the circulation of human babies and in the elderly, perhaps because the latter are less synchronized with their socioecological yearly cycles. Cycles such as the year and one or several transyears may have competed throughout evolution and may have become stronger at the time when *Acetabularia* developed, perhaps 500 million years ago. In the limited data covering a decade or longer, the relative prominence in this eukaryotic unicell of a transyear is greater in *Acetabularia* than in bacteria. We are dealing, however, with different variables, namely with oxygen evolution in the eukaryote and with sectoring, a probable mutation, in air bacteria, including staphylococci.

In bacterial series, the transyear's amplitude was smaller than that of the biological (calendar) year in five of eight series, in one series the tran-syear's amplitude was only slightly greater and in three series a cis-year (slightly shorter than a year) was found, again only slightly greater in amplitude than the 1-year fit, as summarized in Fig 9. This figure also shows that in a eukaryotic (nucleated) single cell, *Acetabularia*, the trans-year's amplitude is bigger than that of the year in terms of its extent of change. This finding applies to time series that consist of changes (from serially independent studies, each assigned to the calendar date of its midpoint) of circadian MESORs, amplitudes or acrophases.

What we see in the unicell, we can also see in a particularly interesting variable related to biological timekeeping in humans, such that in 15 years of data on the excretion of certain steroidal hormonal metabolites. In this case overall, there is no consistent precise yearly component and just a number of transyearly components, each statistically significantly longer than 1 year ([116, 138]; see Fig. 10a). By contrast to the steroidal behavior in the volumes of urines in which the hormonal metabolites were determined, the 1-year component is most prominent, with a numerically higher amplitude than that of the transyear. We must not generalize, however, as can be seen from

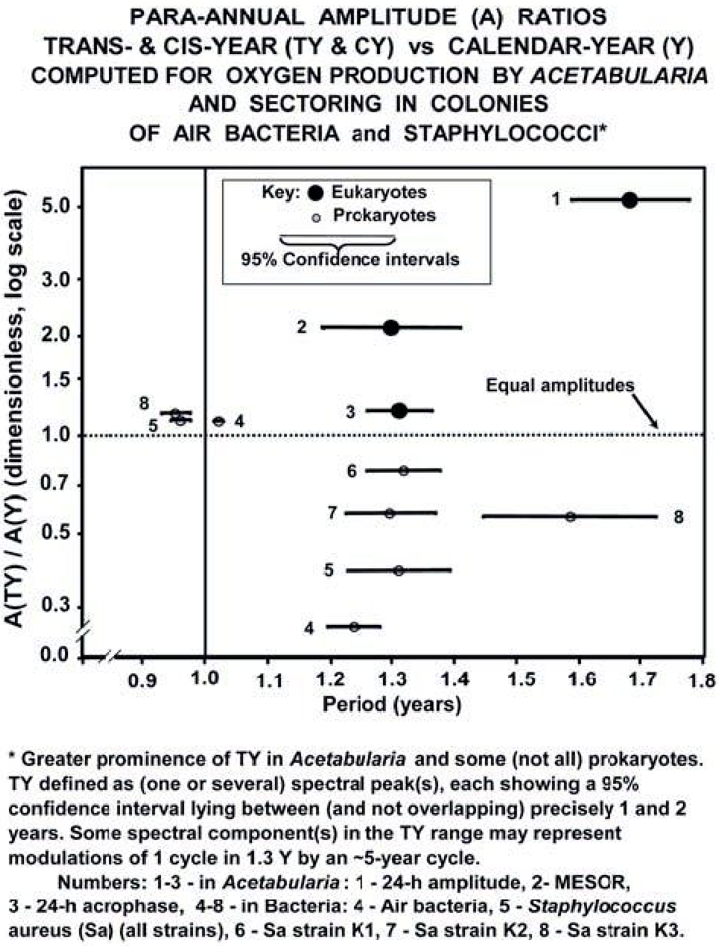


Fig. 10. A spectral component with 95% confidence intervals (CI) between 1 and 2 years, overlapping neither of those lengths, called a transyear, is present early in phylogeny, in a unicellular eukaryotic alga's oxygen production and in ‘air bacterial’ and staphylococcal sectoring, i.e. in probable genetic microbial changes [130].

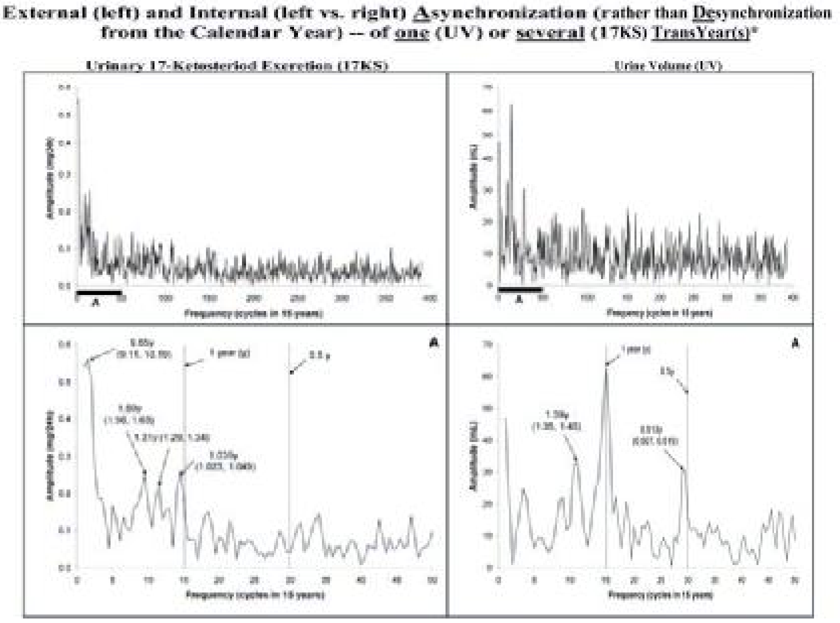


Fig. 11a. Transyears in both a 15-year series of the daily excretion of steroidal hormones (left) and in the urine volume in which these hormonal metabolites were determined (right). Note in urine volume the precise 1-year spike with a much smaller peak corresponding to a transyear. Also note an about-half-yearly component that is not of precisely one-half year length. By contrast, in 17-ketosteroids, there is no half-year or precise year, only 3 transyears, one a near-year, another of about 1.3 years, and a third at about 1.6 years. The time course of the transyears awaits scrutiny by a gliding spectral window. The difference between the two variables may perhaps correspond to a greater degree of endogenicity in the behavior of 17-ketosteroids as compared to that of the volume of urine. An effect of terrestrial magnetism may underlie neartransyears, while heliomagnetics contribute more to ~1.3 and ~1.6 fartransyears.

Fig. 11b, which shows that the behavior of heart rate contrasts with that of blood pressure during the span of adulthood examined. Blood pressure shows a prominent yearly component whereas heart rate shows transyears gaining in prominence with age and on the average a cisyear, which after the age of 40 years becomes a transyear.

Why should we worry about transyears vs years? The two phenomena, transyears, a brand-new finding in biomedicine [129, 136, 137], and the match of the calendar year, extensively explored as photoperiodism, can coexist (Fig. 11c) and if so can amplify each other when they are in phase, i.e. when the peaks occur at about the same time (Fig. 11d, left), and cancel each other out when the peaks occur about 180 degrees apart, in antiphase (Fig. 11d, right), also shown as simulations (Fig. 11e). Initiations or exacerbations of disease, even sudden death, and remissions of disease may conceivably relate to such interaction between two or more near-matching but distinct periodic mechanisms in the circulation or in variables influencing the circulation for which heart rate and blood pressure may be markers if they are not etiologically involved. It will be important to seek mechanisms with periods that are close in length but sufficiently different to augment each other or cancel each other out, as seems possible for the components in Fig. 11a (lower quarter, left). We have seen a beat ([129, 136, 137]; see Fig.11e) and we can expect, and what is critical, we can test for more and for their consequences, once longitudinal series are continuously collected, an urgent task.

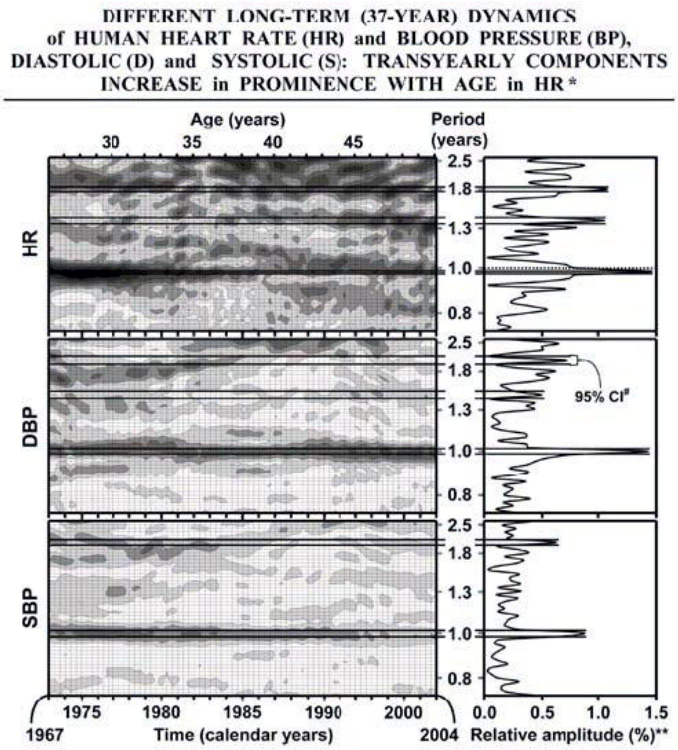


Fig. 11b. Different behavior of heart rate (HR) (top), as compared to blood pressure (BP) in the same subject (middle and bottom), or in urine volume and in the urinary excretion of 17-ketosteroids of another subject (Fig. 12a). Note in the global spectra (right) that the horizontal lines delineating the 95% CIs of spectral peaks do not quite cover the dotted line corresponding to precisely 1 year in the case of HR but do so in the case of BP. This finding based on a data series accumulated over 37 years constitutes a model provided by one of us (RBS) for the need of individualized lifelong monitoring of various psychophysiologic functions. While for HR the largest global peak is a cisyear, the gliding window shows that with advancing age, the period lengthens into a transyear.

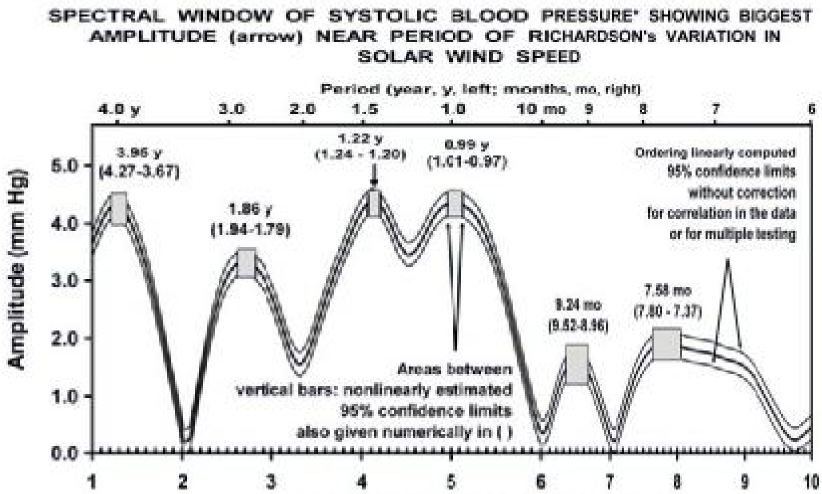


Fig. 11c. In this figure, the presence of a ~1.3-year component was tested and found in human systolic and diastolic BP and HR records from self-monitoring kept by four subjects and thereafter on many more (not shown), to see whether there may be a correspondence with a similar component reported to characterize velocity changes in the solar wind [136, 137]. The results for all subjects support the proposition made earlier that components characterizing physical environmental variables may have a counterpart in the human circulation. The sun affects biota, non-photically as well as photically, at several frequencies as illustrated in other figures and elsewhere, including with the known yearly cycle another distinct one of ~1.3 years, (i.e., ~70 weeks or ~500 days), a putative signature of Richardson's circa-rhythm. Vertical lines bracketting spectral peaks represent 95% CIs for the periods, assessed by nonlinear least squares. It is narrowest for the highest peak at ~1.22 year (95% CI: 1.19; 1.25). This non-photic cycle in human systolic BP is dissociated from the strong satellite-recorded component in the solar wind analyzed for a matching span, which had a non-overlapping 95% CI extending from 1.47 to 1.85 years. The cycle in the systolic BP of GSK, however, closely resembled the ~1.3-year cycle in solar wind available for a longer span (1994–2003), which extended from 1.20 to 1.41 years.

The about-weekly, decadal and a broader spectrum of cycles and sampling designs

The story of the competition between the transyear and year is similar to that between the week and near-week. Both the near-week and the transyear are built in, as shown in a variety of ways, including close but different lengths as suggested, if not established, by non-overlapping uncertainties (95% CIs) of the objectively determined cycle lengths. The analysis of long serial data on populations and individuals has shown about 10.5- and/or 21-, and/or 50-year and about 500-year cycles. All of these cycles

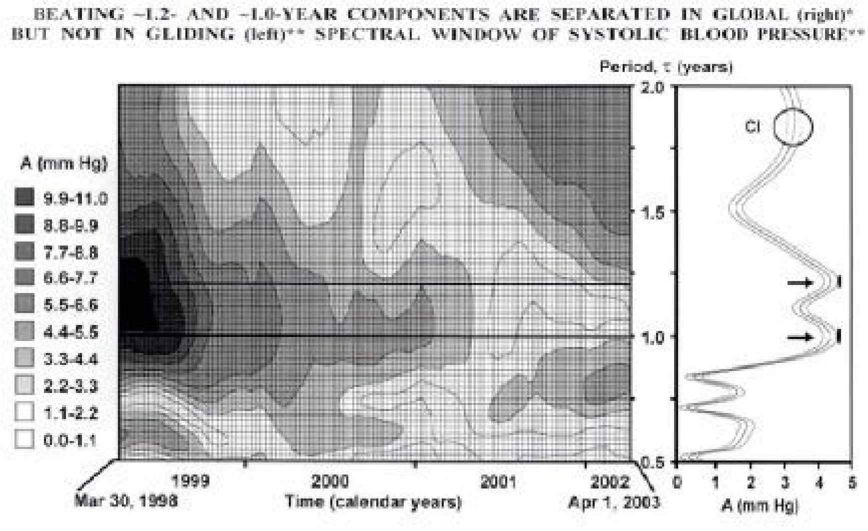


Fig. 11d. Beating between 1.0- and 1.3-year components leads to reinforced and cancelled oscillations alternately as a function of time.

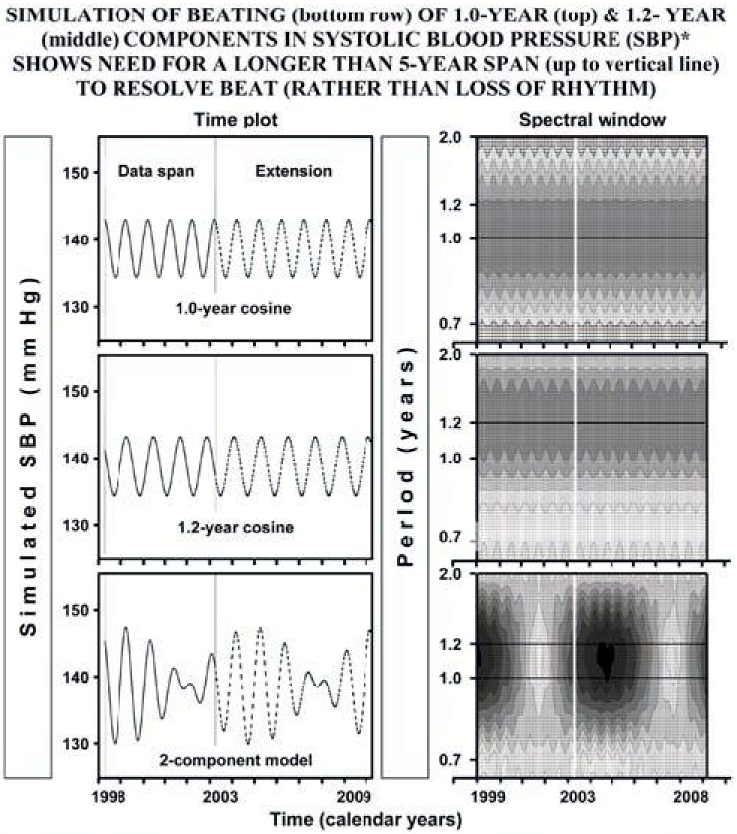


Fig. 11e. Simulation of beat between two signals with closely related periods. .

may be found as different components in the same individual or population variable, such as hormonal metabolites, blood pressure or heart rate measured around the clock for up to one or several decades. Any beating consisting of cancellations and augmentations cannot be detected in cross-sectional studies, where many people are studied for short times, with sampling designs that ignore the rhythms relying on imaginary baselines. For chronomic maps, in turn, that are pertinent to any study, there is a need to monitor at least some individuals longitudinally for decades or preferably for lifespans.

A consensus of the meeting in Moscow [116] concerned the need for government institutions to take charge of the monitoring by especially devoted subjects to enable them to continue systematic monitoring preferably for their lifetime, and to enable others or their families to start monitoring preferably from birth or at whatever age volunteers become available. As put by a journal editor, we need not be 'flying blind' [147], not knowing what happens today in terms of external–internal interactions. We monitor space weather but do not yet use it because biological effects are not popularized or believed to be insignificant and controversial. Current medicine has not yet realized that 'hypertension', and probably many other symptoms, constitute an intermittent condition, even under treatment (Fig. 12), and any effect of magnetism [128] sounds far-fetched. Rather than calling itself 'evidence-based', it should be called time series-lacking, spotcheck-based, flying mostly blind medicine, opening its eyes but for a few seconds, for the spotcheck. This applies, first and foremost, to the clinical trials that accordingly cannot 'see' more than the 'glimpse' provided by each individual, the thousands of participants notwithstanding.

N.K. Malinovskaya et al. [148] reported that the response to changes in the terrestrial magnetic field of seven healthy volunteers 18–39 years of age, as compared with that of 42 patients 53–76 years of age, was different when gauged by melatonin in

24-hour urines. Along a scale from 'calm' through 'disturbed' to 'stormy', melatonin excretion of the elderly patients was higher during a calm magnetic span than during a disturbed or stormy span. In the younger group, melatonin excretion was lower for both extremes vs. the disturbed, presumably usual geomagnetic index. An age effect will also have to be considered [149].

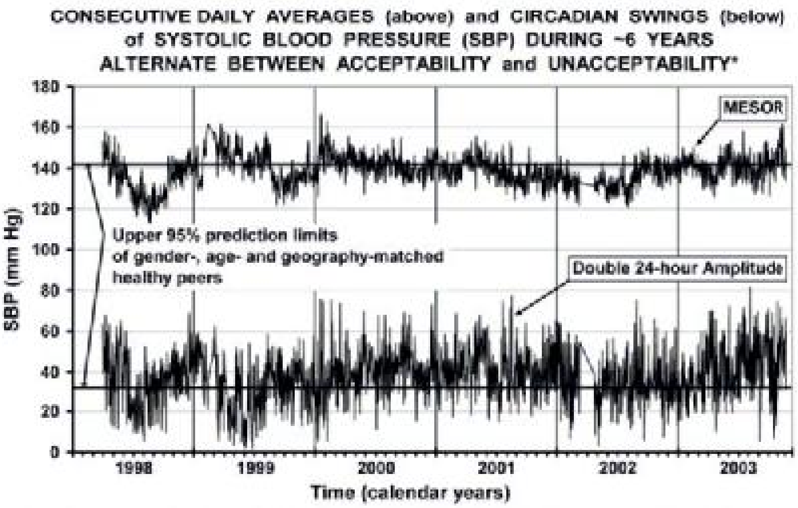


Fig. 12. Even in the absence of changes in treatment, systolic MESOR-hypertension and circadian hyper-amplitude-tension, as gauged by the MESOR (top) and double amplitude (bottom) of systolic blood pressure, respectively, are time-varying phenomena. The dots corresponding to 1-day intervals of data collected half-hourly are sometimes above and sometimes below a reference value developed from peers of the same gender and age. Such variable behavior, even in the absence of changes in treatment, strongly suggests the need to develop inexpensive tools to continually assess and interpret blood pressure behavior so as to adjust treatment as necessary.

C.A. Shemerovsky [116] reported that the West solar physicists are practically absent at medical meetings, this year's meeting in Moscow involved solar physicists to a considerable extent but that can still be improved upon (Table 7). It is good to see substantial cooperation on chronomes in an integrative context in a country devoted to the study of non-photic as well as photic cycles, with many enthusiastic scientists active in it. One outcome of this meeting could be the purchase of monitors for use by university medical students serving as test pilots for the transyear.

Considerable attention is now focused on the effect of geomagnetic fluctuations on biological objects. Most works describe clinical and statistical data on the effect of geomagnetic fluctuations on humans. There is evidence that the incidence of cardiovascular events increases during geomagnetic storms [150-153].

Enhanced geomagnetic activity induced pronounced alterations in cardiomyocyte ultrastructure. During phase Cl, ultrastructure of mitochondria did not significantly differ from that under normal conditions. The mitochondria were equally distributed in cells, sometimes they concentrated in the perinuclear zone. Polymorphism and swelling of organelles and clear-cut duplication of the outer mitochondrial membrane were seen. Some mitochondria demonstrated thickening of the outer membrane with ruptured fragments. Cristae were dense and partially fragmented. Matrix in most mitochondria was dense, although some mitochondria were clarified.

TABLE 7: Cooperation among physicians and/or other biologists with physicists has begun in Russia; currently at 10.4%*: it requires transdisciplinary intensification, as does the use of inferential statistical methods by physicians, biologists and physicists alike.

Presented by:	No. of abstracts	Percentage	Total, %
Physicians	114	54.1	81.1
Biologists	49	23.2	
Physicians and biologists	8	3.8	
Physicists	18	8.5	8.5
Physicists and physicians	7	3.3	10.4
Physicists and biologists	11	5.2	
Physicists, physicians and biologists	4	1.9	
Total	211	100	100
Inferential statistical methods were applied in	36	17.1	100

Mathematical analysis revealed a significant ($p<0,05$) positive correlation between contractile force developed by LV and RV and mitochondrial volume ($r=0.76$ and $r=0.81$, correspondingly), which was described by the following formula:

$$\boldsymbol{y=b+x^m},$$

where b=218 and $m=0.05$ for LV and b=24.6 and $m=9.55$ for RV.

Phase A2 was characterized by pronounced changes in myocardial ultrastructure. The cardiomyocytes membrane was loosened, and the integrity of its outer leaflet was disturbed. Arcades filled with mitochondria and pronounced intercellular edema were seen. The cytoplasm demonstrated individual striated lipid deposits. In most cases, the nuclear membrane was invaginated. Sometimes chromatin margination and its focal washout were noted. The capillary walls were thickened and sometimes surrounded with a collagen sheath. The number of lysosomes increased compared to the previous day. The myofibrils had pronounced homogenization foci. The intercalated disks were thickened and their boundaries were blurred. Myofibrils were edematous and fibrous. Focal lysis, breaks of myofibrils, and invaginations of the nuclear membrane were characteristic of phase A2. Most mitochondria were markedly swollen; the structure of their outer membrane leaflet was disturbed. Some mitochondria had vacuolated matrix. Many mitochondria were destructed and degraded. The cristae were strongly fragmented; the number of cristae in a representative mitochondrion or their total number in a representative TEM image was 2-fold lower that during phase Cl. MEEC decreased 2-fold (from 3.9± 0.8 to 1.9±0.2). Swelling of mitochondria, fragmentation of cristae, decrease of their number, vacuolation of the matrix, destruction and degradation of mitochondria were characteristic of phase A2. The volume of mitochondria markedly increased compared to phase Cl, and the correlation between mitochondrion volume and contractile forces of LV and RV became negative (r=-0.73 and r=-0.81, correspondingly, both remained significant), which attested to further increase in the volume of organelles and the drop in contractile force of the heart.

The number of vessels surrounded by collagen sheaths increased during phase B2. Cell nuclei with chromatin margination and partial matrix washout were noted. During the daytime, the number of primary and secondary lysosomes and glycogen content in cardiomyocytes increased. A characteristic feature of this phase was widening of the sarcoplasmic reticulum. Mitochondrion volume decreased in comparison with the initial phase of magnetic storm, but was higher than during the abatement phase. No correlation was revealed between mitochondrion volume and contractile force of the heart, the latter gradually decreased.

Correlation analysis revealed a strong and significant positive correlation between mitochondrion volume and serum content of free fatty acids ($r = 0,998$; $p < 0,0l$). Taking into consideration that the correlation coefficient between the content of free fatty acids and the number of cristae in an average TEM pattern was $r = -0.988$, and that the number of cristae closely correlates with mitochondrion volume ($r = -0.95$; $p < 0,05$), one can conclude that free fatty acids suppress energy production in mitochondria by inducing their swelling and spatial separation of thcir cristae. This inference is also corroborated by correlation between mitochondrion volume and MEEC ($r = -0.92$; $p < 0,05$).

The unidirectional character of changes in living organisms induced by magnetic storm is confirmed by a significant correlation between myocardial MEEC and LMPC of hepatocytes (r=0.977; p<0,0l). Taking into consideration the reaction of lysosomal apparatus of cardiomyocytes and cardiac contractile function to geomagnetic storm, one can conclude that decrease in EMPC attesting to condensation of lysosomal membranes, cut down participation of these organelles in the processes of intracellular regeneration. Stabilization of lysosomal membrane impedes the effect of lysosomal hydrolases, which among other functions initiate the release of mitochondrial DNA and promote reproduction of mitochondria [151].

It is noteworthy that in nocturnal and morning hours during phase C2, the increase in the content of free fatty acids disturbed permeability of lysosomal membranes (correlation coefficient between the content of free fatty acids and LMPC (r= 0.949; p<0,05). During phase B2, the sign of correlation changes (r= -0.929; p<0,05), which means that lysosomal membranes are stabilized by free fatty acids. In the periods when free fatty acids produce this effect, the number of mitochondria drastically decreased, and most of them degraded. MEEC and $MEEC_{TEM}$ decreased more than 2-fold: from 3.9±0.8 to 1.3±0.4 and from 19.3±4.9 to 8.7±2.1, correspondingly.

Therefore, one of the effects of magnetic storm on living organisms is stabilization of lysosomal membrane. This conclusion is supported by the existence of a strong negative correlation between Cp index of geomagnetic activity and LMPC (r=-0.977; p<0,0l). Analysis of correlation between Cp and LMPC carried out during a period of one year revealed a non-linear interdependence of these indices described by a power function:

$$y=bx^m,$$

where 6=31.5 and m=-0.268.

Hence, enhancement of geomagnetic perturbations is accompanied by a decrease in lysosomal membrane permeability, which is especially pronounced during strong geomagnetic fluctuations. Free fatty acids belong to the main intermediaries in the membranotropic effects of electromagnetic radiation, and their influence undoubtedly depends on the phase of intrinsic physiological rhythms of entire organism and its target organs.

Biological variables sampled mostly daily with variable density (from half-hourly sampling to once or twice a day) for 6 or more (up to 36) years longitudinally, on the same individual, exhibit reproducibly changing chronomes (structures in time) consisting of 1. probabilistic and other chaos, 2. trends and 3. a broad spectral element. Components in the spectral region of about 1.3 years correspond roughly to the periodicity of 1.3- to 1.6-year length in the solar wind [134, 135, 140], herein called the transyear. Thus, there can be two or more distinct components in the about-yearly region of biological spectra, one component at a trial period of ~1.3 years in length, and sometimes in some variables, among others, another component of ~1-year length. We here summarize two kinds of information, one event-related, the other cycle-related. The event-related findings consist of the statistically significant alteration of the circadian acrophase of intracardiac pressure by magnetic storms, just as they may be altered by the lighting regimen or by the availability of a restricted diet, more obvious factors [154]. The circadian acrophase differs with statistical significance, with a near-antiphase of circadians in the profiles during a 3-day span with stormy geomagnetic activity on the one hand, as compared to similar profiles during relatively quiet conditions on the other hand, in three other seasons as well as in the same season 4 years earlier, when data collected over a single day also differ in terms of MESOR and circadian amplitude. Differences in MESOR and circadian amplitude from season to season are part of an about-yearly variation.

We herein also report on a transannual vs. circannual cycle in intracardiac pressure of different comparable groups of rabbits sampled under comparable conditions in the laboratory in four seasons (Table 8). We do so by the rejection of the zero amplitude assumption from the fit of both a 1.0 and a 1.3-year trial period and of any period between these trial periods, that cannot be distinguished from each other by the criterion of amplitude because of the brevity of the series which hardly covers a single cycle and the presence of trends stemming from cycles with lower frequency that will inflate the amplitudes of the low-frequency region artifactually. It is noteworthy, however, that the acrophases are more tightly clustered at the 1.3-year than at the 1.0-year trial period, covering 36˚ vs. 46˚ with 360˚ equated to these periods, respectively. In view of the difference in trial period, the range of acrophases spans apparently the same duration in years. Although data collected over several years will be needed to distinguish between the circannual and transannual components, it is noteworthy that the error in the acrophase (the dispersion) is slightly smaller for the transyear than for the calendar year.

TABLE 8: Transannual vs. circannual cycle in intracardiac pressure of different comparable groups of rabbits

		Summary at 1.0 year	Summary at 1.3 years
PR	P	Amplitude ± SE	Acrophase ± SE
12	<0.001	16.5±1.8	-324°±9
6	<0.001	10.8±1.7	-336°±13
9	<0.001	2.5±0.3	-309°±8
10	<0.001	4.9±0.6	-300°±7

In current moment there is a urgent necessity of detailed researches in area of chronostructure of rhythms and morphology of cardiovascular system and their modifications under action of the external environment factors.

The effects of social phenomena or variations of natural external synchronizers, such as the rhythms of solar radiation and geomagnetic field variations, lead to a similar response in biological systems, namely adaptive stress.

J.B. Burch et al. [156] and A.Weydahl et al. [157] had earlier reported a decrease in human urinary melatonin in connection with heightened geomagnetic activity. Bardassano et al. observed a reduction in synaptic ribbons of pinealocytes of rats during geomagnetic storms, compared with quiet days [158]. Sliwowska et al., [159] using [^{125}I] melatonin for receptor autoradiography, report on immunoreactive neurons in the hypothalami of sheep as targets for melatonin.

The circadian acrophase differs with statistical significance, with a near-antiphase of circadians in the profiles during a 3-day span with stormy geomagnetic activity (fig 13) on the one hand, as compared to similar profiles during relatively quiet conditions (fig 14) on the other hand, in three other seasons as well as in the same season 4 years earlier, when data collected over a single day also differ in terms of MESOR and circadian amplitude.

Differences in MESOR and circadian amplitude from season to season are part of an about-yearly variation. Our results allow the underlying mechanisms of morphofunctional modifications of heart activity, controlled by time factor, to be determined. Magnetic storm modulates morphological and functional state of the heart and the related systems. Changes in cardiomyocyte ultrastructure induced by changes in geomagnetic activity were studied in experiments on rabbits. We describe a possible mechanism underlying changes in cardiac activity in intact animals induced by geomagnetic perturbations. The most pronounced alterations of cardiomyocyte ultrastructure were observed during the major phase of magnetic storm.

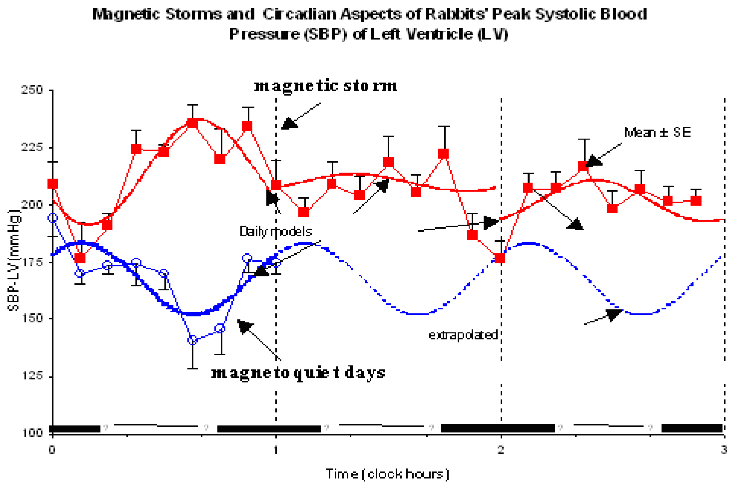


Fig. 13. Near-antiphase of circadians in the profiles during a 3-day span with stormy geomagnetic activity

The MESOR and circadian amplitude were both lower for pineal mealtonin and higher for hypothalamic melatonin on the stormy vs. quiet days. There was a statistically significant inter-dian difference in parameters (M, A, f) of the circadian circulating corticosterone rhythm among days 1-3 but not among days 5-7.

The very small amount of melatonin in the hypothalamus notwithstanding, a circadian melatonin rhythm was earlier demonstrated in this gland and had been shown to differ both in the hypothalamus and in the pituitary in its timing vs. the pineal [160, 161]. A lead in phase of the hypothalamic melatonin rhythm was also found in this study, although the effect of a phase difference in the Wistar rats studied herein was smaller than that found in the spontaneously hypertensive stroke-prone rat of dear Kozo Okamoto [160, 161].

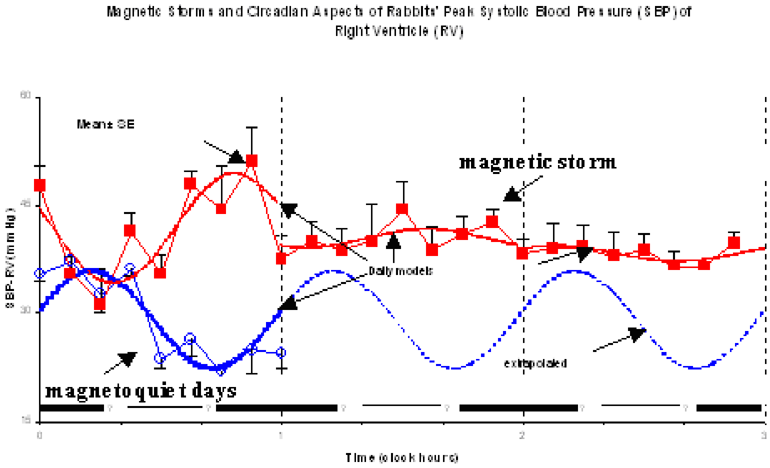


Fig. 14. Near-antiphase of circadians in the profiles during a 3-day span with stormy geomagnetic activity

Whether melatonin in the hypothalamus is derived from the pineal or locally or from elsewhere, multiple hypothalamic interactions – time-qualified feedsidewards [162], rather than time-unqualified feedbacks or feedforwards, may be involved. The adrenal cortex responds directly to melatonin in vitro circadian periodically and responds, also in vitro, via an effect upon pituitary ACTH secretion. The pineal, hypothalamus and adrenal cortex may all be activated by magnetic storms. The almost certain, indirect or direct, involvement of the hypothalamus in situ, shown perhaps for the first time, in Table 1, is in keeping with the findings of the role of emotions associated with both this structure and magnetic storms [162]. The shake-up of adrenal cortical secretion, with ubiquitous central and peripheral effects, provides a mechanism for the varied associations of magnetic storms as well. The manifold associations reported on mood, affect, religious proselytism, wars and cardiovascular pathophysiology now have a plausible mechanism [163-166].

The use of rooms with staggered lighting, beyond investigations of the variables here studied may also be of interest to laboratory investigators broadly. The qualification that any transient effects of magnetic storms by night will be missed, because of the antiphasic sampling design, stands, as noted; it is also clear, however, that the effects were sufficiently prominent to be seen by sampling only during daytime.

Still more generally, investigators, not only of pineal, hypothalamic and adrenocortical function, may review geomagnetic activity in past studies, record it at least as dates in publications, and in the future may consult those who predict space weather, which in part drives geomagnetic activity [167-169]. It seems reasonable to suggest that experiments be planned flexibly, so as to be able to postpone the start of a study when a magnetic storm is predicted by planetary K-indices and/or the equatorial Dst index and/or by many other correlated means. Looking at storms' antecedents in the sun before starting a study is an added precaution, complementing the standardization of lighting [13]; it is being practiced by investigators experienced in this field [170, 171].

Incidence of myocardial infarction, sudden cardiac death and far- and near-transyears.

The already-noted offer of a Nobel Prize pre-World War II notwithstanding, post-war Russian heliobiology, concerned with determining the effects of the sun, was greeted skeptically in the USA even post-war. Two large studies in the US on solar activity and mortality , and a search for the association between magnetic disturbances and mortality [172, 173], reported no solar effect, perhaps since the observation span was too short, assessing less than one ~10.5-year solar cycle and hence not permitting proper (chronomic) analysis, i.e. of any influence of cycles that are one or several decades in length and that may also differ in terms of geographic/geomagnetic locations [174-176]. M. Feinleib and B.J. Lipa had thoroughly analyzed their results that were at variance with the evidence reported in part earlier and later (Fig. 15a; see [176]), in similar and other contexts elsewhere [111-113, 174-176]; see Fig. 15b).

B.J. Lipa et al. [173] rightly left open the question whether the lack of an effect in their studies was related to the circadecadal solar cycle stage or cycle number. Thus by implication, they allowed for the roles of variability in time (read periodicity), as well as in space (e.g. geomagnetic/geographic latitude [177]). Subsequently, the analysis of data from Minnesota collected during 29 years, covering several solar

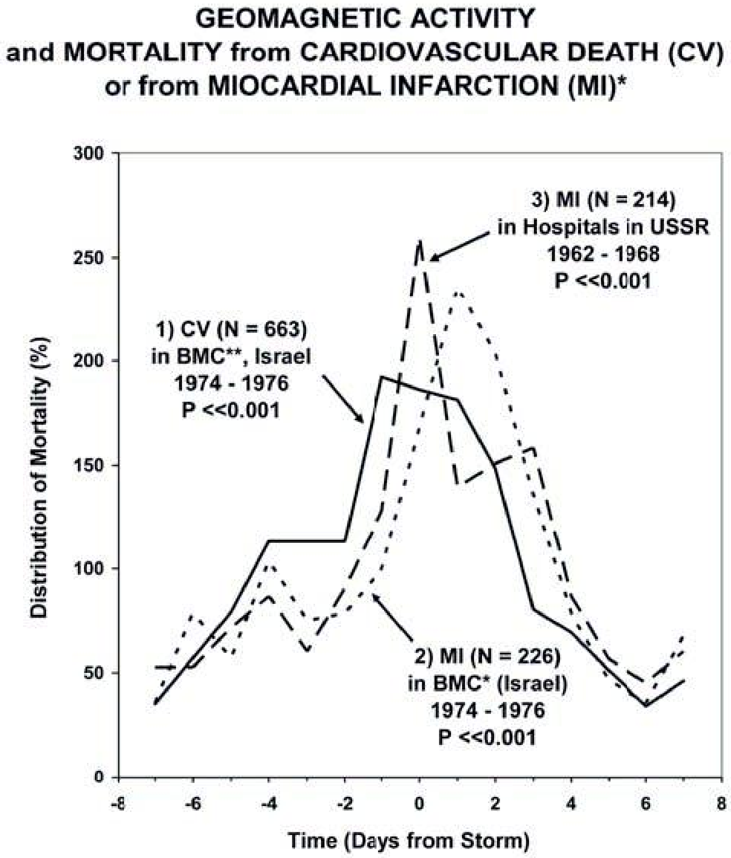


Fig. 15a. By superposed epochs, Eliahu G. Stoupel [176] documented a consistent association of excessive geomagnetic activity with cardiovascular disease in data from the 1960s and 1970s in two geographic locations. While there was a difference between the patterns of all cardiovascular disease, on the one hand, and only myocardial infarctions, on the other hand, note the P<0,001 in each case for the association of vascular disease with geomagnetics.

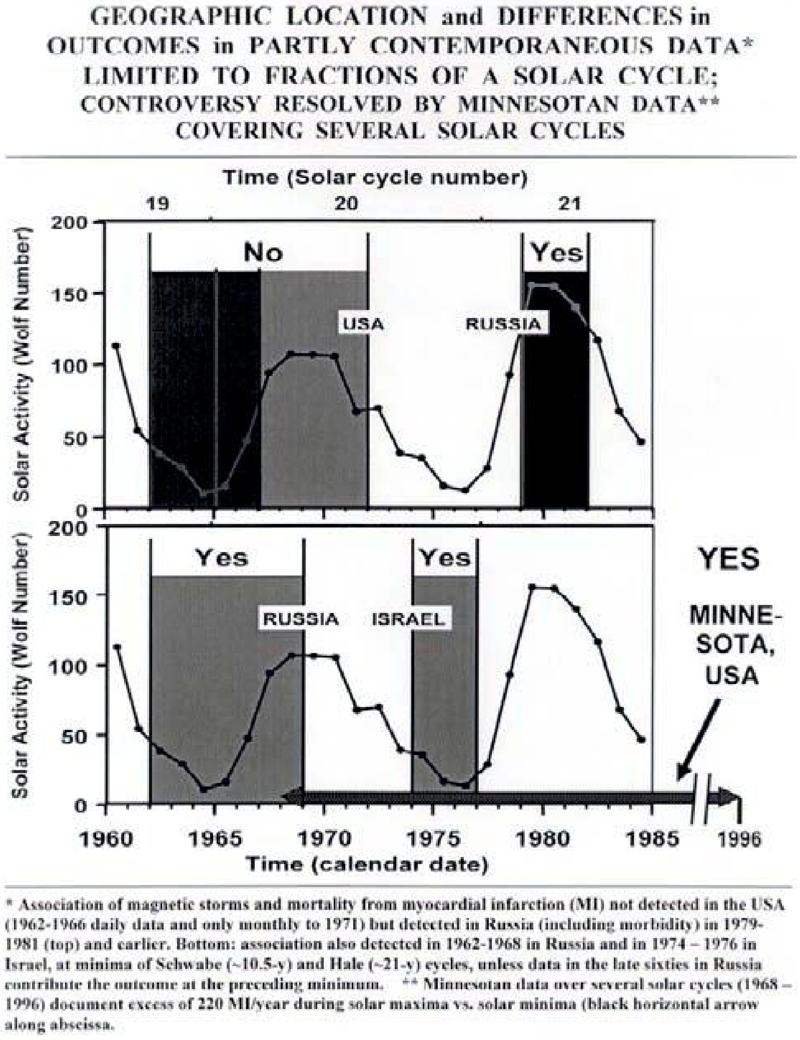


Fig. 15b. A controversy conceivably based on geographic/geomagnetic and other differences in mortality from cardiovascular disease. ‘No’ indicates the failure to detect an environmental effect. ‘Yes’ stands for the detection of an effect. Shading indicates span covered by the data. Results in Fig. 15a (briefly summarized again below on the left) are at variance with results in the USA (above on the left) [128].

cycles, indeed revealed an excess of 220 myocardial infarctions/ year during years of solar maximum, if one averages over the entire time span (Fig. 15c).

Differences with solar cycle number, e.g. among consecutive ~10.5-year cycles in Wolf's relative sunspot number have indeed been found in the case of mortality from myocardial infarctions in Minnesota ([90, 178]; see Fig. 15c). Geographic/geomagnetic differences may also play a role ([90, 178]; and in Fig. 15b). Much ‘secular’ (read unaccounted-for) variation may also be associated with solar cycle stages and/or, in any event, with patterns remaining to be mapped. Cases illustrating changes within a solar cycle from its minimum to its ascending stage are reported when effects in the minimum could not be confirmed in the ascending stage.

Thus for human neonatal blood pressure, a difference in the circadian amplitude between babies with a positive versus a negative family history of vascular disease (that was statistically significant in the solar minimum) could not be confirmed subsequently and prompted us to start focusing on the cosmos [179]. Likewise, adult human circulating melatonin showed at middle latitude a half-yearly modulation by night only during the solar minimum but not in the ascending stage thereafter [180].

Two thousand years ago, Hippocrates reportedly associated thoracic pain with sudden cardiac death (SCD) [181]. In 1707 and again in 1718, Giovanni Maria Lancisi [182, 183] (cf. [184]) published a scholarly, all-encompassing monograph on sudden death; and in 1917 Heinrich Ewald Hering published a book

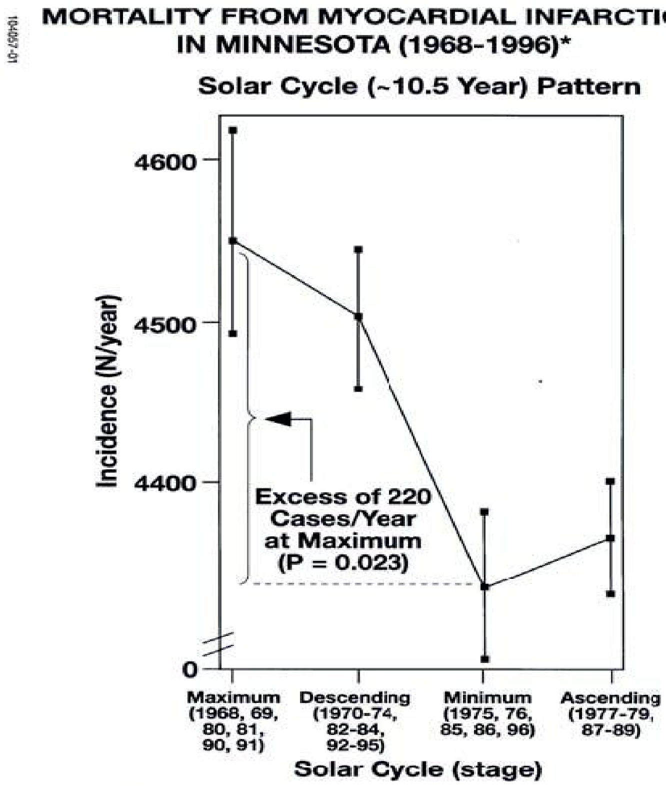


Fig. 15c. During years of maximal solar activity, there is an about 5% excess mortality (220 cases per year) from myocardial infarction in Minnesota (1968–1996) as compared to years of minimal solar activity.

on "death within seconds, with special reference to fibrillation" [185]. The topic remains of interest as an entity in its own right, although the suddenness of the death is differently described by different authors, with the International Classification of Diseases, 10th revision, now referring to death within up to 1 h from the start of symptoms to the terminal event [186-188]. The forensic pathologist, however, in the case of an unwitnessed death, may use the definition of sudden death for a person known to be alive and functioning 24 h earlier, and this is acceptable to scholars in the field with proper qualification. “To the best of my knowledge” is accordingly included in the wording of death certificates. It seems reasonable in the future to focus on a subsample of cases (e.g. with cardioverter-defibrillators and/or other monitors) whose premortal records may be studied for antecedents, even when death was not witnessed.

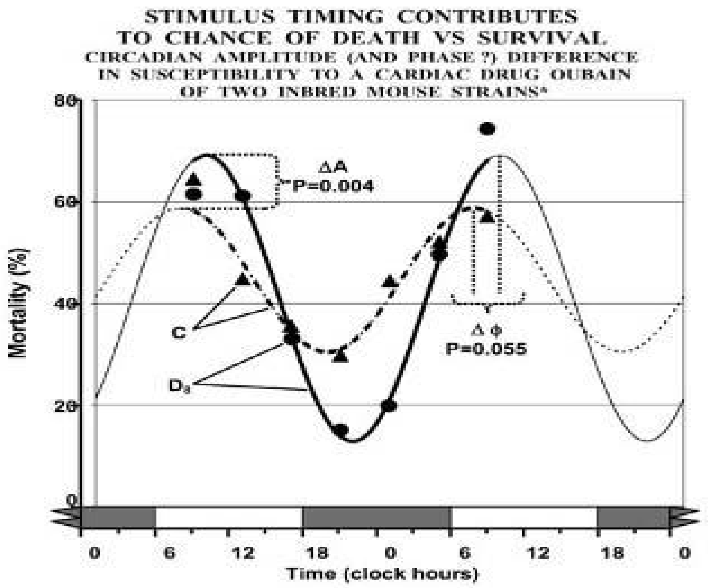
The importance of the circadians was shown in the laboratory by the 1950s, when their stage tipped the scale between death and survival in response to a cardiac drug, Fig. 16 [66, 67].

So do the stages of a much broader time structure to the human response to other stimuli as well, Figs. 17 and 18.

By 1991, it was apparent that the least-squares spectrum of sudden cardiac death (as classified at the time, including MIs) already differed from that of MIs, strokes, cardiac arrhythmia, hypertensive episodes and asthma, Figs. 18 and 19 [189, 190].

Sudden cardiac death, in quotation marks (including presumably MIs), had a somewhat prominent circadiseptan component [190-192], also shown in Fig. 21, in addition to a very prominent about-yearly, Fig. 19, and a lesser about-weekly, Fig. 20, component, which latter it shared with other conditions.

A circadiseptan component of about 15.2 days may be interpreted as reflecting the influence (pull?) at a given time and/or through evolution of a very wobbly magnetic cycle in the environment (see Fig. 21), e.g. in a global geomagnetic index, K_p,



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)

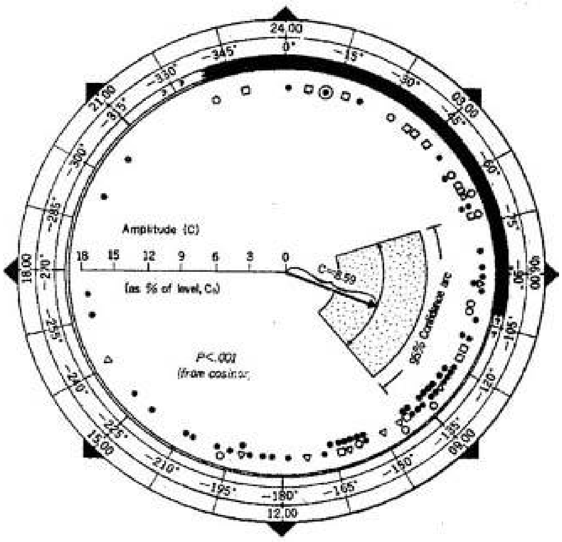
Fig. 16. Susceptibility rhythms to ouabain of two inbred stocks of mice: a laboratory demonstration of the importance of circadian stage in tipping the scale between most animals dying vs. surviving from the same dose of the same cardiac drug, as a function solely of timing in relation to a synchronizing regimen of 12 h of light alternating with 12 h of darkness.

or a local such index, K [192], although the influence of factors of lifestyle, such as alcohol consumption on paydays cannot be ruled out, Fig. 20 [190, 191].

The variability of a large data set on diagnoses made in the context of calls for an ambulance in Moscow, including 71,525 “SCDs” (that included some MIs) during a span of

Circadian rhythm of susceptibility to "death" in human beings

Reveal by 32,892 "natural deaths" over 145 years



Mortality category	No. of cases	No. of (C, ϕ)	Symbol for acrophase
Pediatric	21,673	12	○
Postsurgical	500	1	⊙
Cardiovascular	7,644	9	△
Pulmonary	9,357	12	□
Cause unspecified	393,718	54	•
Cosinor of above	432,892	88	

Fig. 17. Circadian rhythm of susceptibility to "death" in human beings [66].

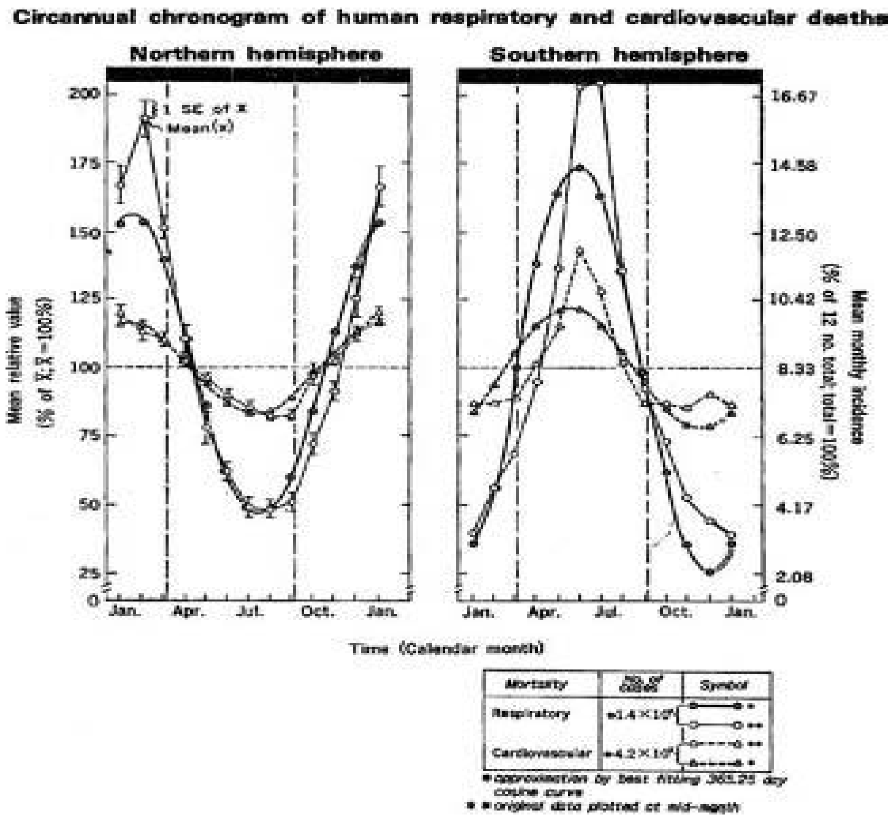


Fig. 18. Circannual chronogram of human respiratory and cardiovascular deaths. Chronograms of human mortality population rhythms reveal highest incidences during winter irrespective of hemisphere. Least-squares approximation of the monthly means by a 365.25-day cosine curve accurately reflects waveforms for the northern hemisphere. Slight discrepancies between original data and approximating curve for the southern hemisphere due to small number of samples available [66].

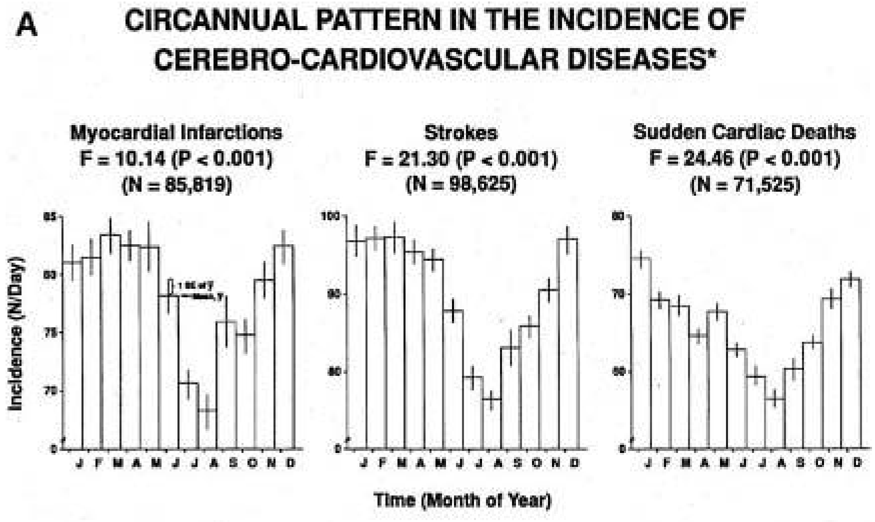


Fig. 19a. From a total of 6,304,025 ambulance calls to Moscow hospitals between January 1, 1979, and December 31, 1981, 85,819 cases of myocardial infarctions, 98,625 cases of strokes and 71,525 cases of "sudden cardiac death" (including some MIs) were identified. Their daily incidence shows statistically highly significant circannual patterns with a higher incidence in winter than in summer. This pattern is shared by many conditions, including SIDS. When analyzed more thoroughly, different circannual patterns emerge, for instance, for "sudden cardiac death" [189-191].

intensive solar activity from 1979 to 1981, had prompted us to look into any effects of a turn in the north-south vector, B_z, of the interplanetary magnetic field, as a measure of a magnetic storm [189]. There has been a long controversy about the merits or demerits of a "heliobiology". Its importance was very strongly supported in the Soviet Union and subsequently again fully accepted and highly regarded as a scientific area sui generis in present-day

Russia [11, 112, 193-196]. The effect of geomagnetic activity as such or as a proxy for solar effects upon human mortality from MI and other cardiovascular conditions is in keeping further with a summary of mortality from different causes in Europe in the 1930s [174, 175] and ourselves [189, 195 204].

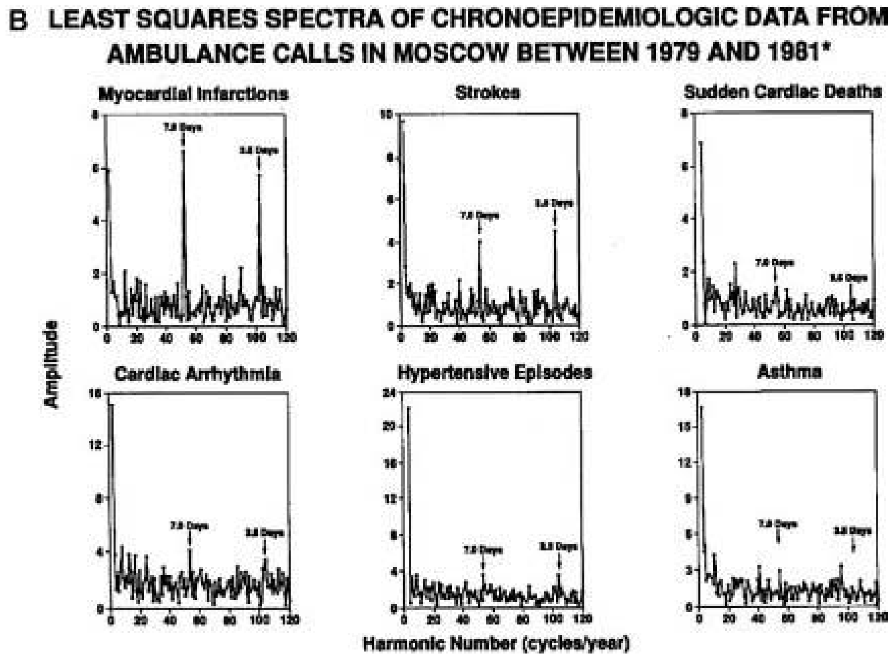


Fig. 19b. An overall view of the variability in the daily incidence of myocardial infarctions, strokes, cardiac arrhythmia and hypertensive episodes, reveals, in addition to the anticipated circannual peak, shown on the left of each graph, also components of 7 and 3.5 days, some rising very prominently above the general level of the spectrum, but much less so for “sudden cardiac death” and asthma [189, 190, 193].

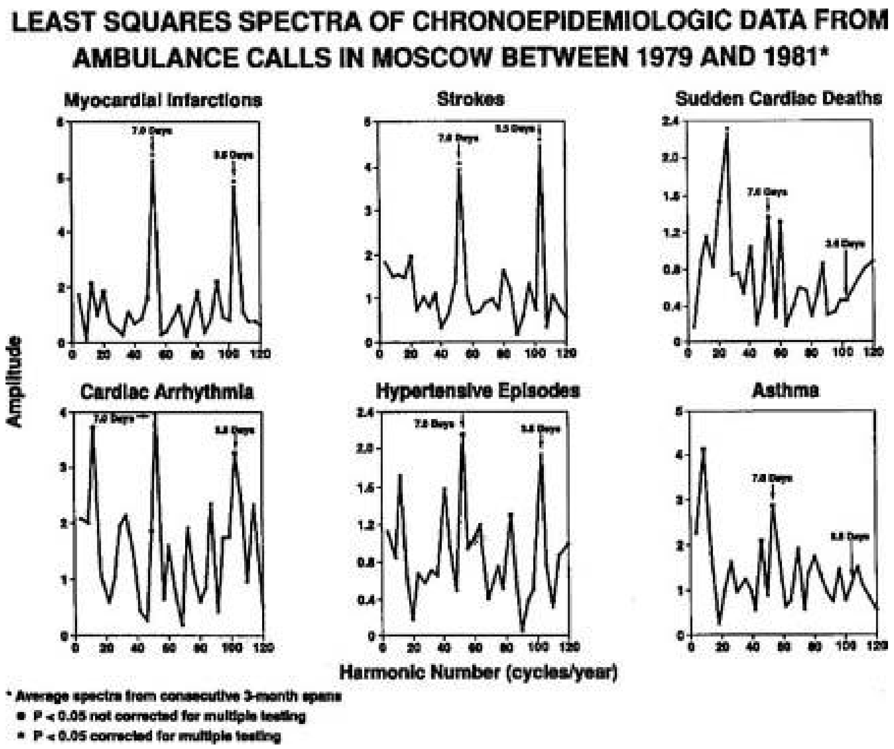


Fig. 20. Averaging the least-squares spectra of Fig. 14b computed over consecutive 3-month rather than 1-year spans allows the test of statistical significance of the peaks in the spectrum. In most cases, after correction for multiple testing, the circaseptan and circasemiseptan components remain statistically significant. For "sudden cardiac death", a circadiseptan component is most prominent [113–118, 130, 193].

Our finding of a near-week of 6.75 days [116, 119, 121] rather than a precise week [122, 123] in geomagnetics, first in the planetary index, K_p [116, 119, 121], was confirmed [108] and extended to the antipodal index aa [109] by physicists and then by ourselves [121], all as a counterpart of a built-in biological week [41, 111-113].

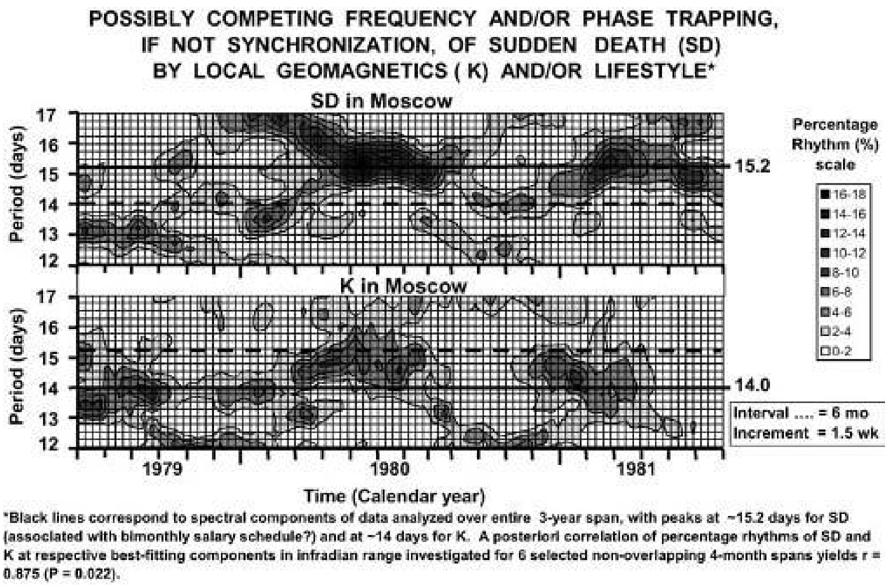


Fig. 21. Wobbliness of the about 2-week variation in “sudden cardiac deaths” (top) and the local index, K, of geomagnetic activity (bottom), revealed by gliding spectra wherein data in a 6-month interval are progressively displaced by a 1.5-week increment. Note that detection of the about 2-week component is not consistent throughout the 3-year span. A possible resonance with occasional frequency trapping between the multiseptans of the local geomagnetic activity index, K and “sudden cardiac death” is suggested by the more prominently expressed (darker) about half-monthly variation in “sudden cardiac deaths” observed when this component is also detected in the spectrum of K [191, 192].

This led us to the postulate that the rotation of the earth around its axis is not the only environmental cycle built into life on earth. Not even the extension of the time structure to include the time it takes for the earth to revolve once around the sun and the consequent seasonal changes with photic effects exhaust the list of putative built-in cycles. The finding of the near-week in our environment prompted us to seek an environmental counterpart for each biological cycle, preferably one anchored in the genome, as suggested for the week by free-running [41]. Vice versa, we began to seek a biological counterpart for each more or less consistent, albeit wobbly environmental cycle, characterizing non-photic as well as photic solar activity [116, 47, 129, 205].

Analyses are summarized, whose fourth to sixth sites in the second section shows that under sudden cardiac death in three of the six geographic/geomagnetic regions examined, there was only a spectral component of a calendar year in length. In these locations (North Carolina, Tbilisi and Hong Kong), the point estimate of the τ may differ slightly numerically from the exact year's length, but the 95% CI in each case covers the precise calendar year length.

Almost certainly, as seen in many other instances, with an increase in length of a given series, a spectrum can be very greatly changed and we must not be speculating herein. For physics, K. Mursula and B. Zieger [176] proposed that an about 1.3-year component changes to an about 1.5–1.7 years oscillation with each subsequent solar cycle. In pursuing this possibility, a further analysis of a 131-year series of the geomagnetic aa index then revealed the near-transyear as well, and as in the case of K. Mursula and B. Zieger [176], these components were intermittent; our analyses in sections of fixed rather than solar cycle lengths do not suffice to rule in a relation to changes in the solar bipolarity [121, 128].

The data, however, suffice to point to the need for further scrutiny of any regional differences, even within the same country (USA), where three different situations are found with North Carolina having only an about-yearly component, Arkansas having both components, the year and a candidate transyear, with nearly equal amplitude, and Minnesota having just a transyear in the limited data available.

Geographic/geomagnetic differences have also been documented for the circadidecadal phase of human neonatal body weight, with a near-antiphase between 2,150,122 newborns in Minnesota and 1,166,206 newborns in Denmark [206]. Whether local geo- or atmosphero-magnetics and/or other factors account for this difference and others, remains an open question. It seems reasonable to suggest that one may withhold inferences in any aspects of heliobiology until multiple locations are scrutinized for as long a span as possible, for a given pattern; one must also define the length of the time series examined, underlying a given finding so that it can be further qualified when added longer time series become available. In the context of broader evidence, it seems reasonable to postulate that unseen non-photic cycles, that have their origin in the solar wind, for which geomagnetics are a proxy if not cause, contribute substantially but differently to the pattern of human sudden death and to body weight at birth, and that this contribution is also dependent on local factors, possibly terrestrial and atmospheric electrical currents. The role of non-photic cycles in transdisciplinary human affairs is a challenge, for which an atlas in space and time constitutes an indispensable requirement [129], as agreed upon in a series of international consensus meetings [207].

The task of providing the data are the opportunity of national governments and international agencies in a historical context. We have shown cycles of about 50-year length, including one in stroke incidence with similar periods in the Czech Republic and in Minnesota, USA, and supporting data from Sweden, Slovakia and Arkansas, USA [113, 208]. Until governments and international agencies act, action by ministers of health like BF [208] and/or responsible statisticians served us herein. Letters to U.S. state health departments other than those of Minnesota, Arkansas and South Carolina have remained unanswered for weeks and will remain so perhaps indefinitely. Government statisticians will have to realize that they are not only bookkeepers; their opportunities, if not mandates, should include the cost-free provision of dense (when indicated, preferably hourly) data as a minimum and the chronomic time series analysis by themselves of the accumulating records as an optimum. Health care can take stock of cycles which may differently affect MI and SCD in different geographic locations and to a different extent and in a different way in different variables [209]. Much added international research against this background could focus on many aspects of time structure, complementing focus on time of day [210-112] or rather circadian phase [213], day of week or season [212], or rather circaseptan [190] and circannual phase [64, 67, 68, 190], cycles adding to the heart's rhythm [69].

By contrast, in the data from Minnesota, there is only a transyearly component. Fig. 22a shows the actual data: it is difficult to interpret these very low monthly incidences without analyses.

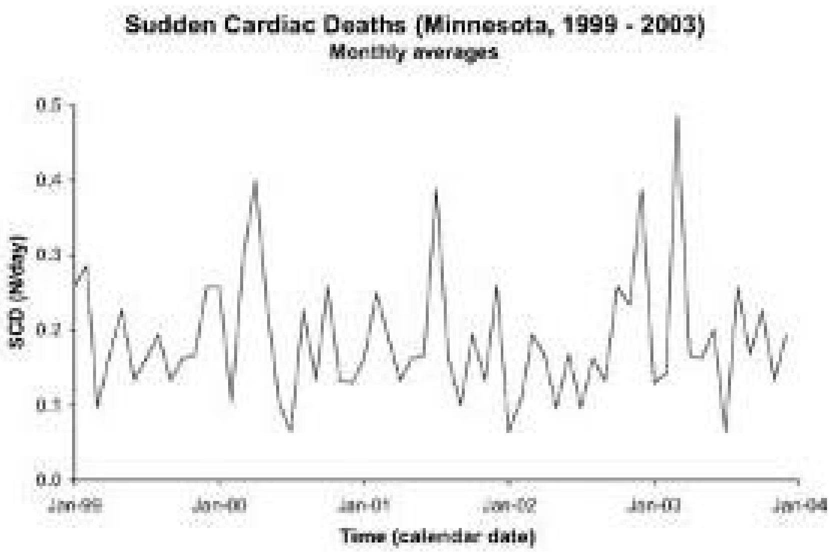


Fig. 22a. Incidence of sudden cardiac death in Minnesota. The naked eye has difficulty in discerning a pattern, yet some peaks occur apparently at intervals longer than 1-year.

Stacking of the data over this period in Fig. 22b results in a zero-amplitude test significant below the 2% probability level. By contrast, as would be expected if a calendar-yearly component were absent, the fit of a 1-year cosine curve to data stacked along the calendar year in Fig. 5c does not allow the rejection of the zero circannual amplitude assumption (p = 0,171).

In the data from Arkansas and the Czech Republic, there are components with the length of a calendar year, along with a probable candidate transyear. We speak of a candidate transyear when the τ is between 1.0 and 2.0-year length and does not overlap 1-year, but overlaps the length of 2 years. In other words, in the 1999–2003 series, the condition of the 95% CI of the τ not overlapping 2 years is not (yet?) met by transyears in Arkansas and the Czech Republic in the data limited to 5 years, but it is met for the longer series from 1994 to 2003 from the Czech Republic.

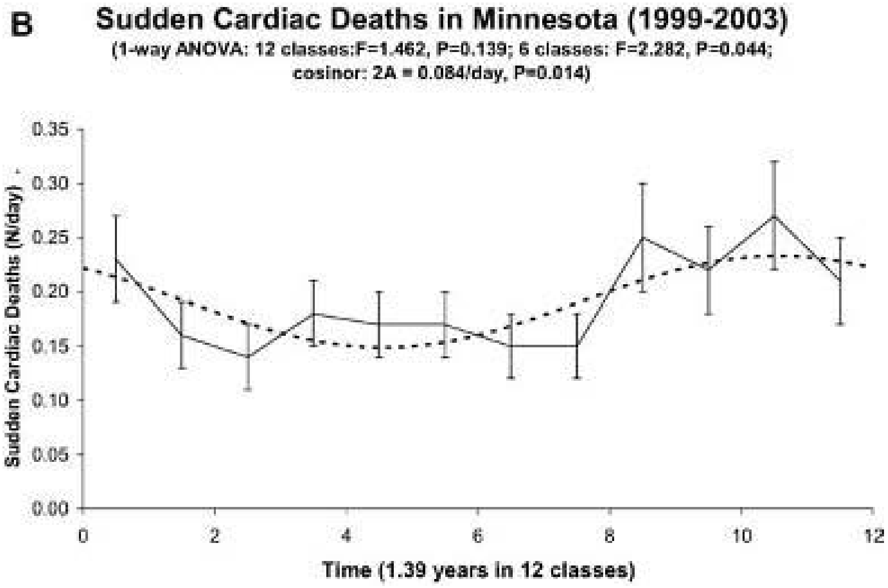


Fig. 22b. The fit of a 1.39-year cosine curve, a period resolved by linear–nonlinear rhythmometry, to the data from Fig. 1a stacked for this transyear allows the rejection of the zero-amplitude assumption below the 2% level of statistical significance.

Mortality from MI shows in turn during 1999–2003 a very prominent circannual component and a much less prominent transannual. In the longer series on MI, also summarized, a near-transyear and a far-transyear (see Scheme 1) are both resolved.

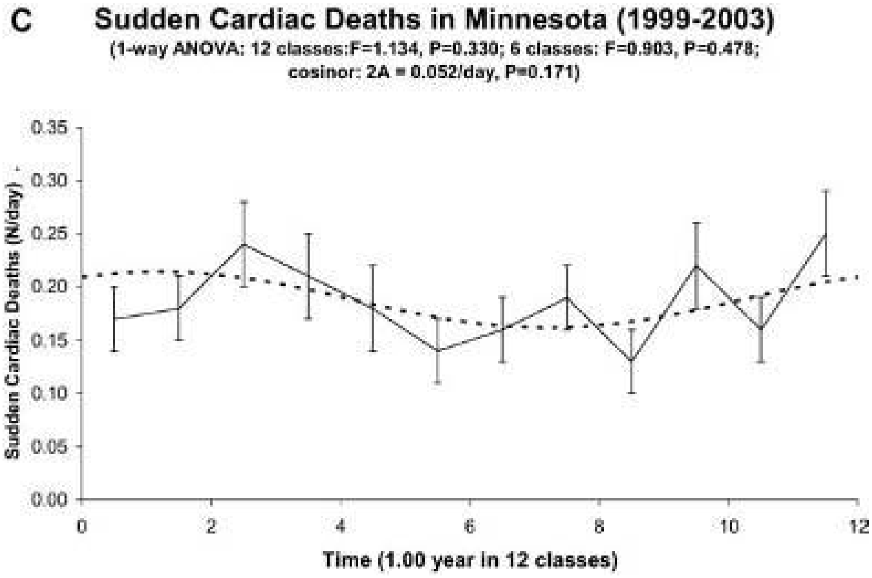


Fig. 22c. Stacking of the data in Fig. 4a for a calendar year does not reveal any statistical significance in a zero-amplitude (no-rhythm) test. This would be expected if only a transyear (Fig. 4b), but no calendar-yearly component characterized the data.

It seems possible that geographic differences may underlie the failure of very thorough investigations in the USA by M. Feinleib et al. [172] and B.J. Lipa et al. [173] to confirm earlier, notably Russian and German studies, and studies in Israel and Lithuania, led with proper documentation by Stoupel. Much more on the effect of magnetic storms or cycles upon human morphology, physiology and pathology has been the subject of nine conferences [207, 214, 215].

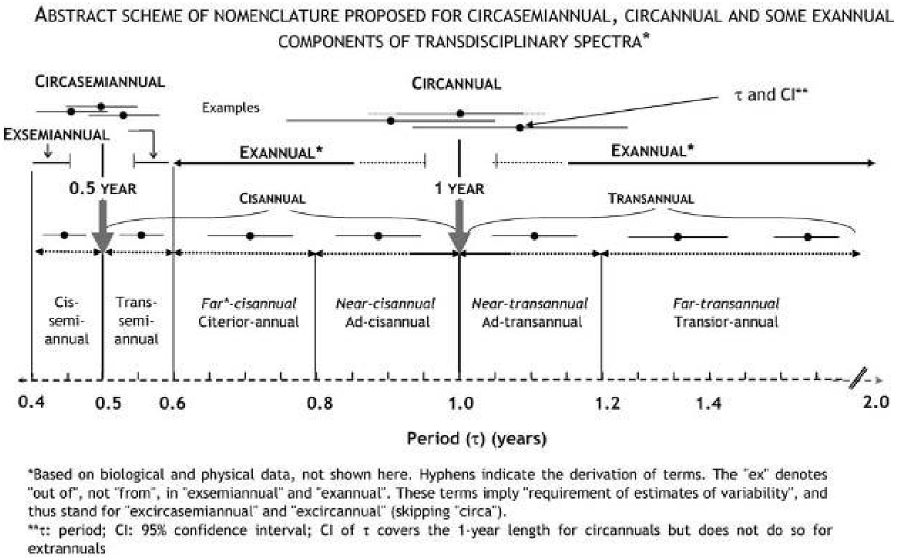


Schéma 1.

It is the more remarkable that during the span investigated for the Minnesota SCDs, in the strict sense, there is only a trans-yearly and no calendar-yearly component detected, notably since for a much longer 29-yearly Minnesota series of MI, the seasonal component was much more prominent than an also-present signature of a non-photic, probably magnetic circadecadal component. A mechanism possibly underlying these associations was found by self-studies, by F. Halberg and K. Otsuka in Fig. 23 [84] in Fig. 24a and 24b and found in the laboratory as well by S. Chibisov [216].

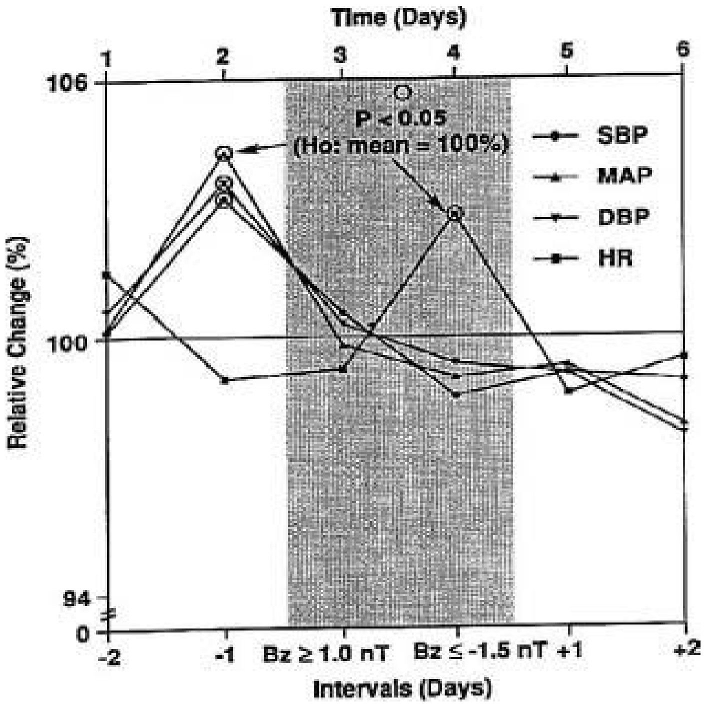


Fig. 23. Influences of magnetic disturbances are extended from pathology to physiology, i.e. to human heart rate, which in the case examined increased during the storm, and to blood pressure, which increased on the day before the storm.

The strongest support came from an approach by subtraction and addition, in an individual or group [217, 218]. In Fig. 23 display a statistically significant increase in systolic, mean arterial and diastolic blood pressure but not of heart rate of a 70-year-old man who monitored these variables around the clock with an ambulatory monitor, mostly at 15-min intervals, between 1987 and 1991 [214].

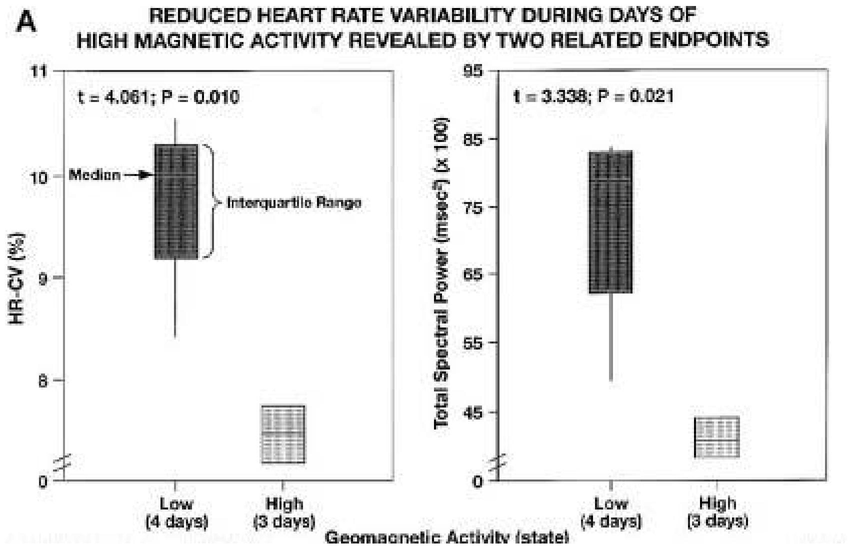


Fig. 24a. Reduced heart rate variability of a clinically healthy 48-year-old man on days of high magnetic activity vs. days of low magnetic activity, assessed longitudinally in beat-to-beat data recorded around-the-clock over a 7-day span and analyzed over consecutive 14.4-min intervals. Heart rate variability is gauged by two related endpoints: the coefficient of variation of R-R intervals (time domain; left) and the total spectral power (frequency domain; right).

The alternative remains that some events in the IMF may precede a southward Bz-turn by chance. That this is not necessarily the case will have to be corroborated in other cases and/or on the same case during added monitoring; if and only if corroborated, one may postulate that blood pressure may respond to an influence from outside the solar system, should the increase in blood pressure at least during certain stages of decadal or multidecadal solar cycles consistently precede the magnetic storm (and may relate to an event eliciting that storm, as well as the increase in blood pressure before the storm).

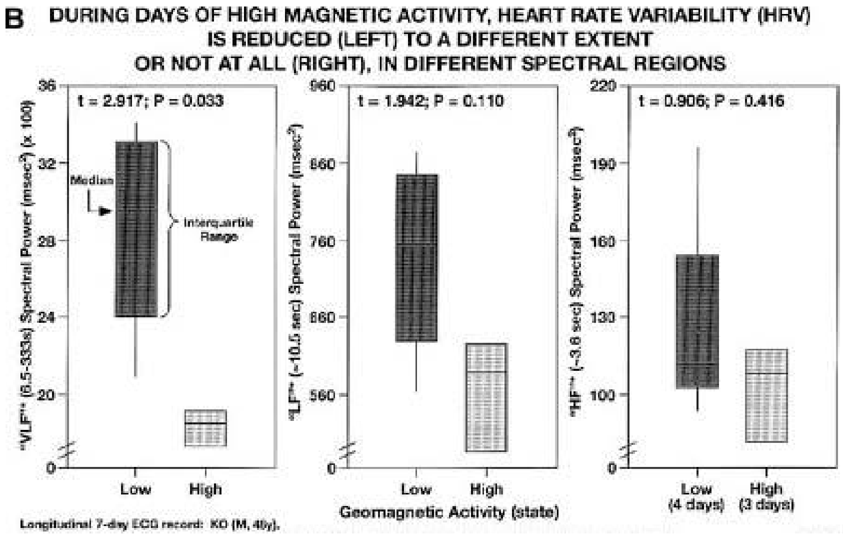


Fig. 24b. During the span examined in Fig. 24a, during days of high magnetic activity, heart rate variability (HRV), in different spectral regions of a clinically healthy 48-year-old man on days of high magnetic activity vs. days of low magnetic activity, assessed longitudinally, is reduced (left) to different extents or not at all (right): the decrease in HRV is more pronounced for periods in the spectral region between 6.5 and 333 s than in other spectral regions.

The results in Fig. 24b has been confirmed on additional cases; it may point to some underlying physiological mechanism responsible for the physiological response to changes in magnetic activity other than the parasympathetic, usually identified with spectral power in the 3.5-s region. References to “high” and “low” frequency are misnomers once it is realized that HRV changes, with the ~10.5-year solar cycle, a frequency much lower than a very low frequency: an "infra VLF" [201, 202].

We now turn from transyears to half-yearly components, long known in physics and rightly used by H. Delouis and P.N. Mayaud as references to estimate the prominence of other components [97]. In human SCD, there are spectral components, with a length on this side (= cis) of the 0.5-year length, with the CI of these components not overlapping the exact half-year. Such half-years differing from the precise half-year, being shorter, were found for SCD in Hungary, the Czech Republic and Minnesota, and (only) during the corresponding spans also in geomagnetics and in the solar wind. Longer series of these physical environmental variables show no cis-half-year, e.g. when the entire available series is being analyzed. Likewise, turning back to the bottom rows, the geomagnetic index K_p and the solar wind speed, show periods corresponding in length to one of those in Arkansas and the Czech Republic, and their CI overlaps even that of the putative Minnesotan transyear of SCD. But these similarities of τs are only hints: As yet the geographic differences are based on much too small samples insofar as SCD is concerned, and larger samples from more geographic locations are indispensable, as are available for MI in Fig. 19.

In the pattern of SCD, when all available series are used, irrespective of geographic location, and the values of each series are expressed as a percentage of the series mean and then averaged, the calendar year component also predominates and the transyear is not seen. This finding underlines the need for more extensive SCD data to find clues as to whether we are dealing only with random chance error or also, as we see for MI in Fig. 24**,** with statistically significant components. Much controversy about heliobiology, apart from small numbers, an argument that has been lad to rest by large numbers for MI, may also stem from a changing relation to geo- and heliomagnetics, as shown by time-varying phase synchronizations and coherences [219].

Different patterns of human cardiovascular mortality may differ from each other, may also differ with time, as do solar-terrestrial phenomena and probably differ with geographic location, a possibility that urgently requires the provision by different governments of data for analysis.

These findings of interest to biomedicine may also serve physics since, as noted, the human time series can reveal dynamics that prevailed perhaps since hominization and the Acetabularian time series allows us to take a look at perhaps 500,000,000 years ago. P.N. Mayaud [220] writes that an important solar noise is still superimposed upon the semiannual variation averaged over 100 years. It will be of interest with the aid of biological findings to see what other components can be lifted from the noise term now that biomedicine provides a 0.42-cis-semiannual component in SCD. These findings need to be aligned with the more precise half-yearly spectral component. The cis-semiannual, but not the average 0.5-year circasemiannual component, may contribute to SCD.

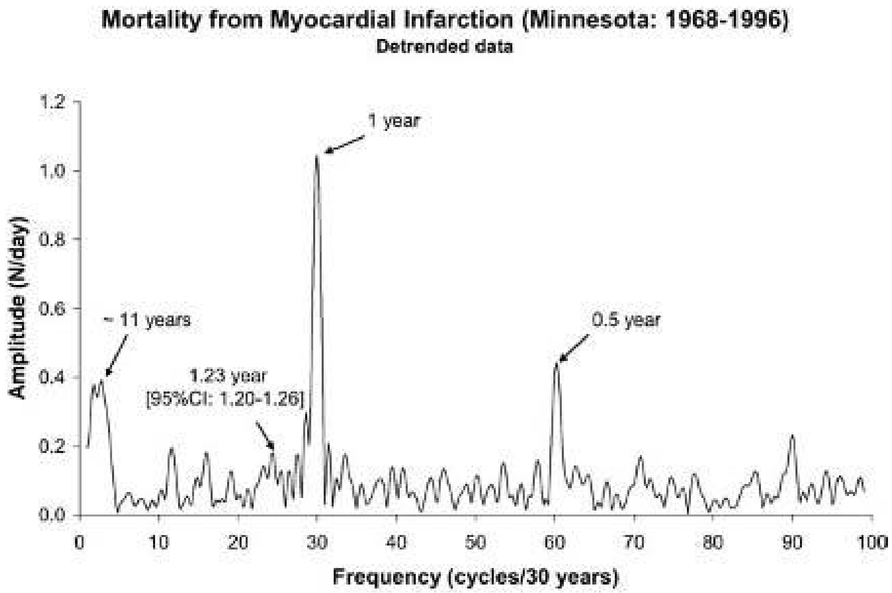


Fig. 25. Clear prominence, in a relatively long time series of myocardial infarctions, of yearly, probably climatic component over any magnetic ~11-year, 0.5-year and transyearly components, the latter with even smaller yet with a non-zero amplitude.

Over three decades ago, by objective curve-fitting the non-random distribution of human mortality along the 24-h scale was confirmed, quantified and extended to human mortality more generally in Fig. 10, and to cardiovascular death in particular, Fig. 26. This was then hardly surprising since by the 1950s we had learned that the stage of a circadian system can make the difference between 75% of comparable inbred mice dying from or surviving a fixed dose of a cardiac drug such as ouabain, Fig. 16. Carrying such laboratory animal experiments to the clinic beyond the circadian rhythm is the challenge of a new millennium. We emphasize the transdisciplinary nature of the problem to which, if geographic differences hold water, both Gilbert’s *terrella*—the large and near magnet earth–and perhaps the huge but far magnet the solar system, and the still broader cosmos, far beyond a single fluid star, such as the sun, all contribute.

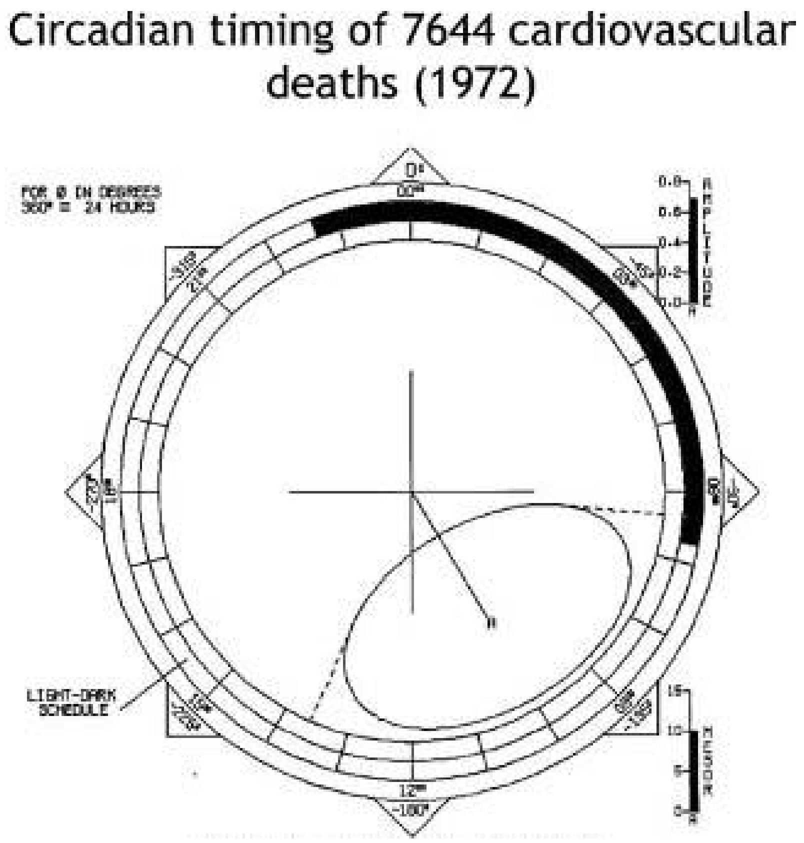


Fig. 26. Cosinor summary of the temporal distribution of deaths along the 24-h scale involving the heart.

With a background in endocrinology, one realizes that the similarity of periods is nothing but a hint, notably of the importance of the phenomenon, whether or not the hint revolves around life vs. death from the same dose of the same agent in the case of the mouse or of a similar condition in the case of humans. Endocrinology also provides a remove-and-replace approach which can be and has been transferred to physics. We have such evidence [217] about the sun's influence upon a biological near-week in human heart rate but not yet for a biological and physical near-half-year and not for near-years.

The time for a transdisciplinary science has arrived, notably if we go beyond cardiovascular disease and start to focus on the human mind and spirit that intensely involves our circulation. An organism is a set of cycles; wherever you cut it, there is both a beginning and an end, with interactions in space-time in between. Chronomics images the cycles in and around us, some seen and very many largely unseen, except for auroras.

Let us turn from the cycles, including different trans-years in natality and death, at the extremes of extrauterine life, to those that form parts of time structures. These consist of many rhythms, probabilistic and other chaos as well as of trends that accompany us and can now be monitored in an increasingly cost effective way. For a health care and for broader science, time-microscopically resolved structures can replace spotchecks or series examined by the naked eye without a transdisciplinary inferential statistical chronobiology and chronomics.

Transdisciplinary atlas of the human noosphere

A transdisciplinary rule of reciprocity of periods in us and outside us is met by cycles of photic origin such as a biological day (circadian) and year (circannual) and by cycles of non-photic origin, such as ~ a half-week, ~ a week, a half-year, a near-year, only slightly longer than a year, perhaps relating to terrestrial magnetism, one (or two) transyear(s) of ~1.3 (and ~1.6) year in length, ~7 years, ~ a decade, ~2 and ~5 decades. The near-match of the solar wind's ~1.3-year, called the transyear, is found in each of over 50 series of human blood pressure and heart rate and now in other series including an endocrine variable. Hints of endogenicity sometimes stem from non-overlapping 95% confidence intervals between transyears in satellite data and in us. The challenges of Gauss, Humboldt, Sabine and Chizhevsky are a systematic biological governmental surveillance starting with blood pressure and heart rate monitoring from womb to tomb, a recommendation submitted to the meeting as a whole for immediate use for detecting an elevated risk of vascular disease, i.e., stroke, that promptly renders chronomic imaging cost-effective, as well as for use in transdisciplinary concerns involving sampling along the time scales already mapped [153, 155].

In *Les origines humaines* ('Human Origins'), Edouard le Roy distinguished two stages in evolution: one starting with the origin of life, the other starting with 'hominization', the appearance of humans [221], who with their language created what we call civilization or culture, if not yet a chronobioethics. Vernadsky used le Roy's concept of the nine (cf. [116–123] and [130]) meetings here distilled, notably [118], noosphere, i.e., the sphere of the human mind as an achieve-seek the inclusion, by a scientific approach, of something ment from the emergence of hominization. Russian scienti-even more critical than the mind, i.e. of an ethosphere fic endeavors aligned this noosphere with the broader [41, 195, 196] biosphere, embracing all living matter on the yet broader A special round table at the March 1–3 meeting [1] was earthly lithosphere, hydrosphere and atmosphere, and the held against the background of an atlas of temporal variations still broader mineralosphere of the cosmos. The actually in natural, anthropogenic and social processes already published on Global Changes of Environment and Climate [196]. A.G. Gamburtsev advocated the extension of this ambitious accomplishment into an international endeavor, which could include health care topics for the individual but could also emphasize diseases of society by focusing on crime and terrorism. Thus, it would be concerned with mapping cycles in data on 'good and bad' customs and habits (=*ethos),* in an ethosphere including spirituality and morality (Fig. 26). By invitation of the participants at the round table, whereby to examine how chronobiology and chronomics could institute international mapping of the cyclic and other dynamics involved in the health and diseases of societies as well as of individuals. Mapping from birth to death, yet to be set up, should include ontogenetic and phylogenetic memories, to eventually serve in dealing with the optimization of ethics.

Chronobiology seeks the mechanisms underlying quasi-reciprocal cycles or rhythms found in and around us. Some seem obvious, like the light-involving, i.e. the photic and thermic environmental vs the biological day and superficially the (again) i.e. photic and thermic seasons vs the biological calendar year. The latter must now be qualified by the transyears. Indeed, unseen, non-photic but assessable cycles are primordial insofar as they are prominent early in life and may be vestiges in us, yet functioning, among others, as ontogenetic and phylogenetic 'memories'. The non-photic cycles include, among many others,

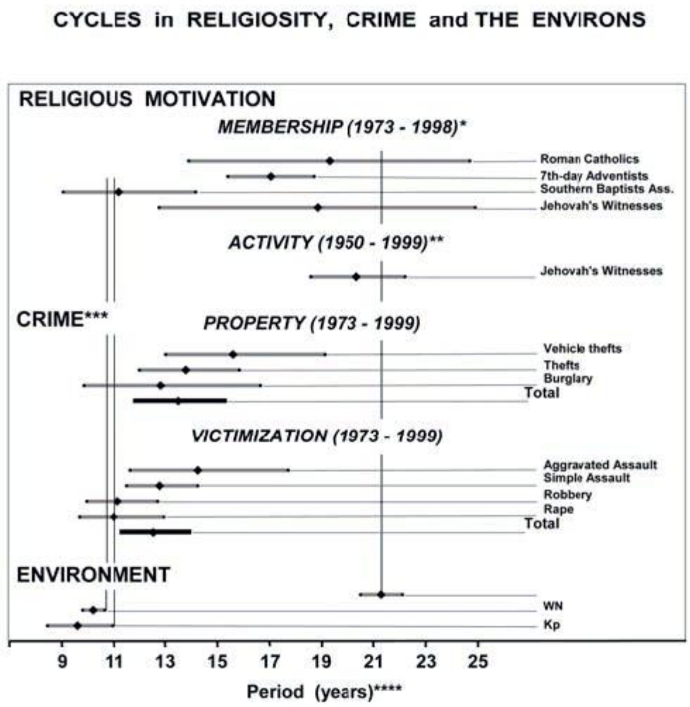


Fig. 27. Cycles characterizing behaviors, ethical and unethical. Data on church memberships are relatively short and their broad 95% confidence intervals contrast with those on time series covering longer spans (on large populations) available to document a cycle in religious activity, i.e. in the motivation to proselytize based on a record covering nearly half a century, and showing a geomagnetic/geographic latitude dependence of the cycle characteristics in the mimicry of a geomagnetic Hale cycle (not shown here) [222]. .

about half-weekly, about weekly, about half-yearly, trans- (beyond) yearly (i.e. slightly longer than a year), about decadal, about didecadal, about quindecadal and even longer about multidecadal cycles of populations. We here propose that their relative importance for a given variable, species, sex, age and other qualification be gauged by amplitude ratios, as illustrated in an abstract manner in Fig. 27 for the case of the week.

The known spectral element of cycles and rhythms covers in frequency 10 orders of magnitude in a human individual and is still broader in populations. Many of the rhythms and/or cycles that underlie life are synchronized; can be phase-shifted by 'switches', i.e. by light–dark and feed–starve cycles; and are influenced by (resonate with) presumably built-in non-photic cycles that can, like magnetic storms, transiently override all other synchronizers for the case of magnetic storms [139].

Special focus on mapping intermodulations of the reciprocal (in the sense of near-matching) internal and external infradian cycles in religious motivation vs crimes and atrocites with ultradian rhythms of the heart, the brain and the endocrines is overdue [223].

The finding of reciprocal cycles around and in us (*omnis rhythmus, omnis cyclus e cosmo*) may prompt the alignment and scrutiny, among others, of interactions among cyclic physical environmental factors and cyclic or other changes in spirituality. Thereby, we anticipate finding an understanding of any physiologic bases of spirituality and thus, perhaps, the possibility to predict and prevent diseases of society, such as crimes and atrocities.

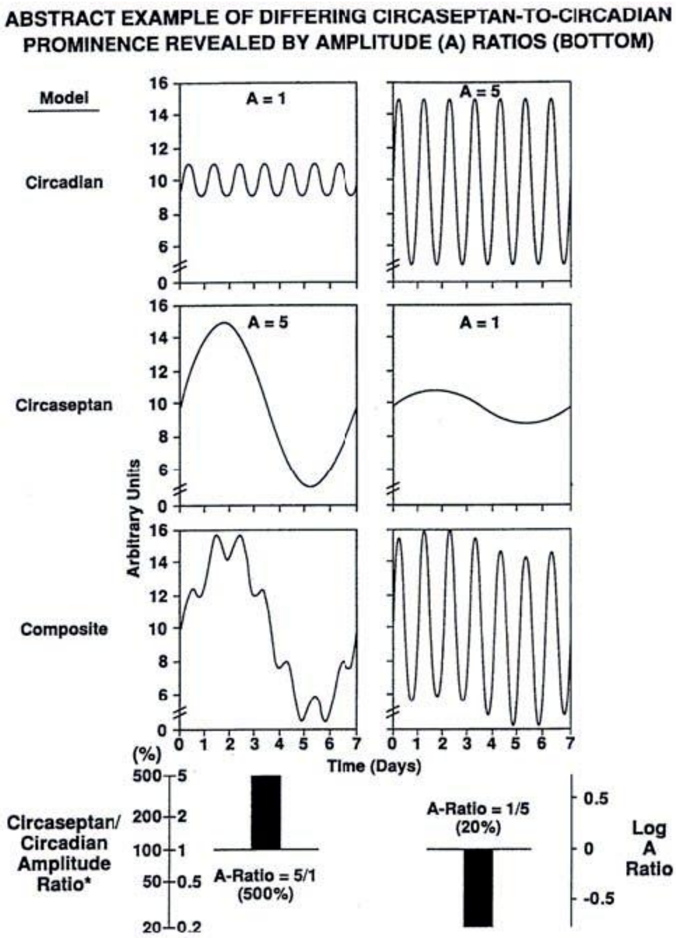


Fig. 28a. Illustrative non-photic/photic amplitude ratio change showing, in an abstract way, the transition from circaseptan to circadian prominence noted in a boy in the first month of life, applicable also, among others, to transyear/year, or 21 year/year amplitude relations.

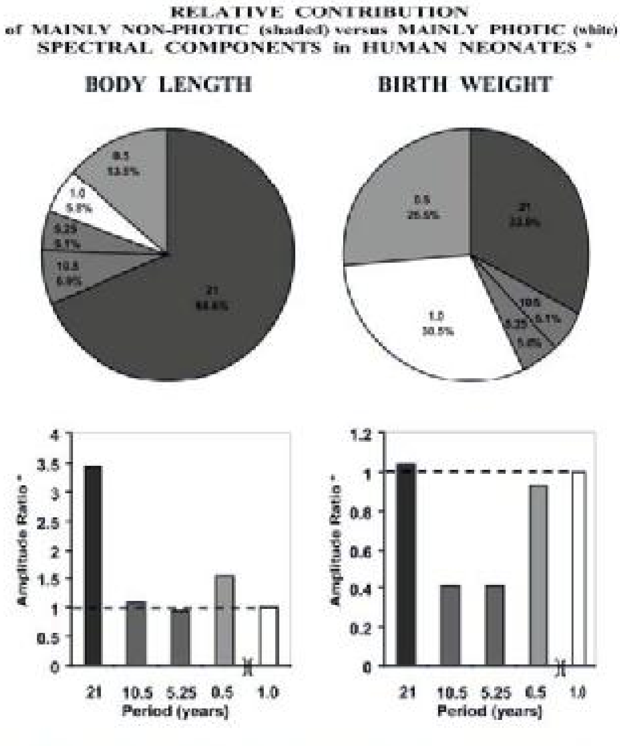


Fig. 28b. An about 21-year component, corresponding to the Hale cycle in length, is the dominant spectral feature in human body length at birth in data published originally from the viewpoint of changes along the scale of a year. Results in keeping with those on other records obtained over spans of up to and over 100 years elsewhere. The circadidecadal component is also apparent in body weight in many large populations.

A scientific optimization is needed and may become possible in endeavors inquiring into where we come from, into where we want to safely go, and most importantly, how we go about life in everyday physiology and psychology, including crime, bioterrorism, and accordingly ethics. An approach here advocated examines pertinent cycles of behavior in us and their visible and invisible counterparts around us, as these relate to many others, also to spirituality. As motivational cycles become in part measurable [223] and are found to be manipulable by physical environmental factors, an optimization may become possible. If so, we may conclude that to the extent that ontogenetic and phylogenetic memories makes us understand where we come from, they may also help us construct a better future not only in extraterrestrial space, the task of a chronoastrobiology initiative, but also on Gilbert's *terrella.*

Baillaud's reflections concerning accepted and controversial lunar cycles, meteorology and agriculture, pertinent to, but beyond the scope of this paper, remind us that Hyde Clarke, in the Railway Register in 1838 [224], first described a cycle in economics that coincided with a cycle in solar activity, in the same year in which Schwabe [226] published data revealing a clear cyclicity in sunspots, but as yet did not dare to write about periodicity until he had assembled several additional years of data by 1844. Biology must also focus on other cycles such as those reported by Pales and Mikulecky of about 500–600 years in human cultural growth [225]. It is only a hint to find a cycle characterizing famous physicians [225] to correspond (in length only) to one of tree ring width [227], and to another in international battles [129], all with overlapping 95% confidence intervals.

The postulate that, just like physical growth, cultural growth does not appear continuously but occurs in wavelike creative outbursts [225], prompted Emil Pales and Miroslav Mikulecky to analyze three sets of famous physicians, 44 of Greek and Roman, 18 of Chinese and eight of Indian origin, living between 700 BC and 1400 AD, tabulated as numbers per century (or half a century for the Greco-Roman data). By periodograms and cosinors, Pales and Mikulecky reported a cycle of about 500 years for the periodic emergence of great physicians in the histories of these three regions widely separated geographically. We confirm the findings of Pales and Mikulecky by linear–nonlinear rhythmometry, for the emergence of great physicians (Fig. 29a) and for the emergence of great historians and poets (Fig. 29b), while to be rigorous, the cosinor, of course, requires the prediction of the period of an anticipated cycle.

Whenever a solar origin is postulated in physics, economics, agriculture or psychophysiology, the postulate of quasi-reciprocal cycles in and around us [90] can be helpful, and indeed some solar rhythms exhibit cycle lengths found in biology and vice versa. But the physicists' records of aurorae and sunspots are not long enough to look for cycles half a millennium in length. It seemed of interest therefore to look again for a proxy marker of solar activity in tree ring widths that cover the past 2000 years or more, as others had done before us. We had analyzed 11 sequoias and had found a period of 534 years as the most prominent feature (Fig. 29c). In data taken from a published graph [228], an about 500-year cycle was also found to characterize the coloring of stalagmites, possibly reflecting changes in earth's subsurface temperature.

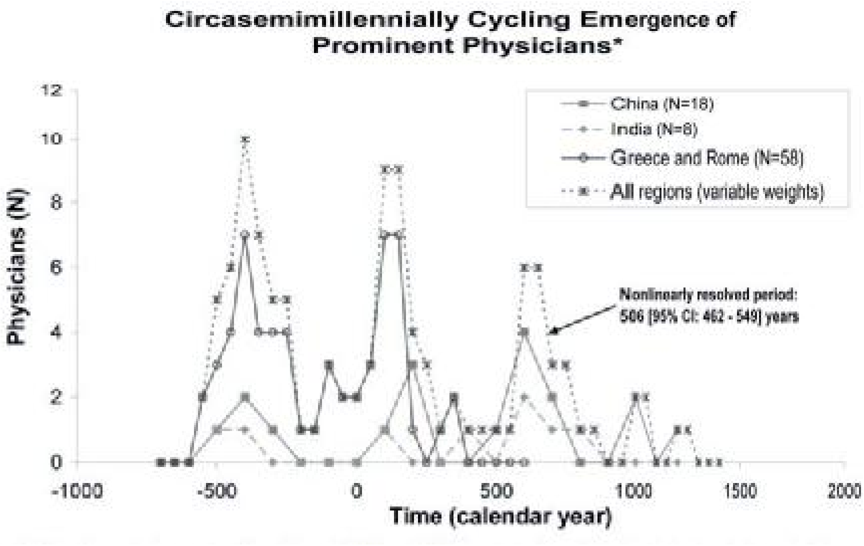


Fig. 29a. About 500-year cycles in the emergence of famous physicians are visible to the naked eye, and seem to be synchronized in three completely different regions. [225]

The average period from a nonlinear analysis of famous physicians from three different areas in our hands was 505.6, with 95% CIs from 462 to 549 years. The average period of famous physicians, historians and poets, and of similar cycles in the Wheeler index of international battles [229], tree ring width and stalagmite coloring was 518.6 years (Fig. 29d). An acrophase chart at this average period is provided in Fig. 9e. The results cautiously encourage us to consider extrapolating backward by the dynamic (read: cyclic) biology of living matter today, to times for which there is no dynamic physical and only a dead fossil record. In so doing, physics could avail itself of biomedicine. Historically, physicists remember the physician William. Gilbert – the author, as regarded by two of their kind [230], of the first scientific treatise. Thanks to Mikulecky and Pales, physics can consider learning how Gilbert's famous predecessors [225] have also served transdisciplinary science, by their very numbers and timing of their cyclic emergence. But the greatest promise for physics and transdisciplinary science is that of finding a scientific solution to bioterrorism, crime and other diseases of society.

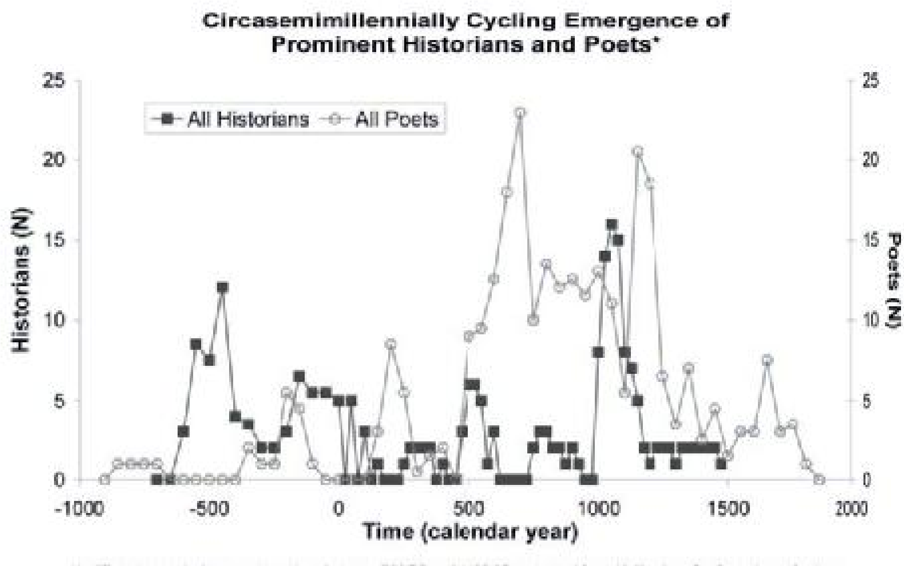


Fig. 29b. About 500-year cycles are also apparent in the emergence of famous historians and poets. [225]

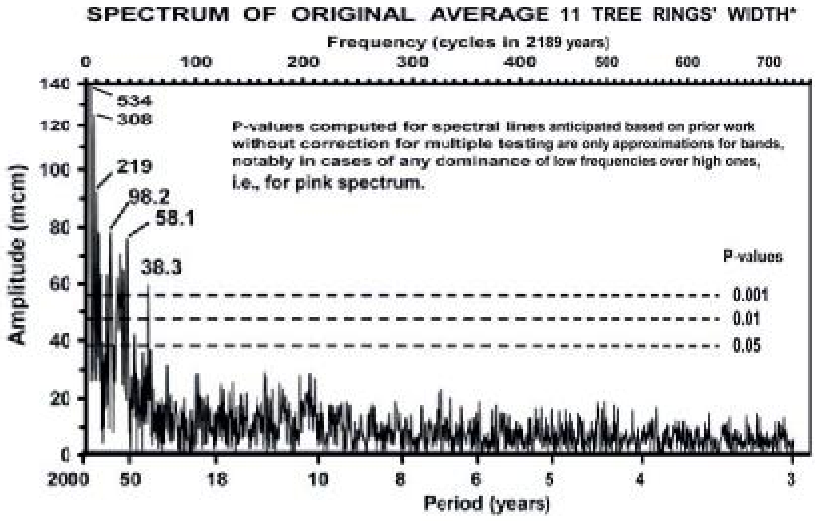


Fig. 29c. Indirect proxy-approximations of solar activity via the effects of climate upon the growth of trees during spans when no other human dynamic indices exist. A cycle with a period of over 500 years here shown was obtained in the course of studies reported earlier [227]. A similar cycle was also 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 [225].

A combination of methods is needed for identifying (read: isolating) many putative effects of our environment, including those of the moon and the sun [199, 200, 232-237] from each other. We are dealing, in part, with a mathematical task that a premature death prevented first Bärbel Schack [219] and no w Alexander Konradov from completing. Lucien Baillaud rightly includes in his review a subtitle "The need for good

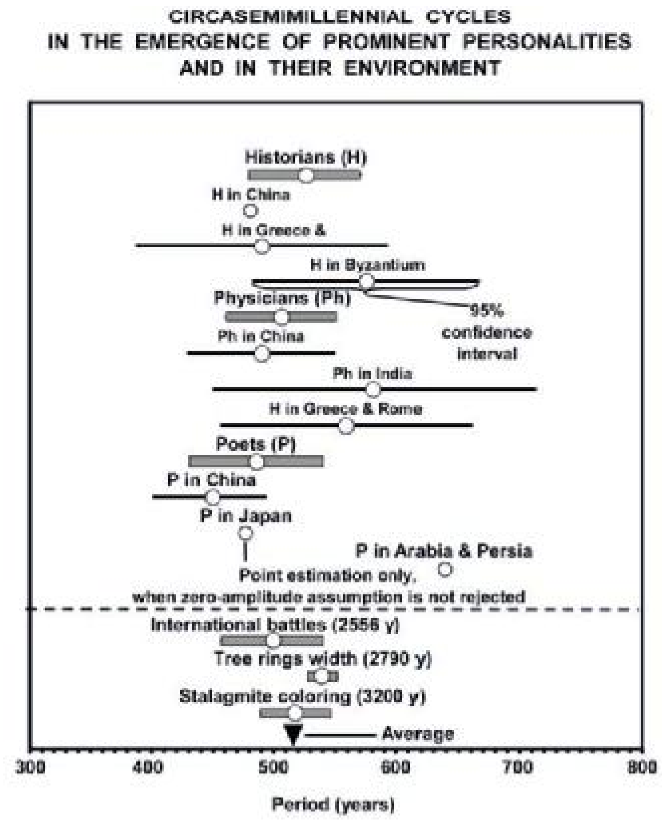


Fig. 29d. Chart of about 500-year cycles in the emergence of great historians, physicians and poets, compared with similar cycles in the Wheeler index of international battles [229] and in two series likely related to climatic changes, namely tree ring widths and stalagmite coloring.

methodologies", which implies biological (remove-and-replace) as well as inferential statistical methods [235]. Investigators in chronobiology and chronomics and in a budding chronoastrobiology should remember Lucien's subtitle [235] unless they wish to share the fate of Molière's Bourgeois gentilhomme [231]: Monsieur Jourdain: ‘‘Par ma foi! il y a plus de quarante ans que je dis de la prose sans que j'en susse rien, et je vous suis le plus obligé du monde de m'avoir appris cela’’. (‘‘My goodness! I've been speaking prose for over 40 years [chronobiology and chronomics: resolving time-varying phase relations and time-varying coherences, with changes in prominence, at multiple frequencies] without realizing it, and I'm infinitely grateful to you for having told me so.’’) (Molière: Le bourgeois gentilhomme, Act II, Scene V).

With available and yet to be extended methods, an atlas of the chronomes is at least as important as the mapping of the genome (Figs 30).

The cycles are the reproducible aspects of the litho-, hydro-, atmo-, mineralo-, bio-, noo-and ethospheres, and hence this aspect of chronomes is essential, not only for genomics but far beyond, as a sine qua non for the intact maintenance of life on earth. Chronome mapping has to be a nationally and internationally coordinated effort in eve-rybody's service. It can immediately change a health care based on spotchecks for disease into one of chronomically examined time series, seeking to detect risk elevation before the fait accompli of disease as a new indispensable imaging.

In comparing the yield of chronomics with that of genomics, e.g. in the service of cardiovascular disease risk assessment, genomics as yet has not equaled chronomics in detecting silent risks that can be substantially lowered for a cost-effective prehabilitation. This aspect of chronoastrobiology is critical

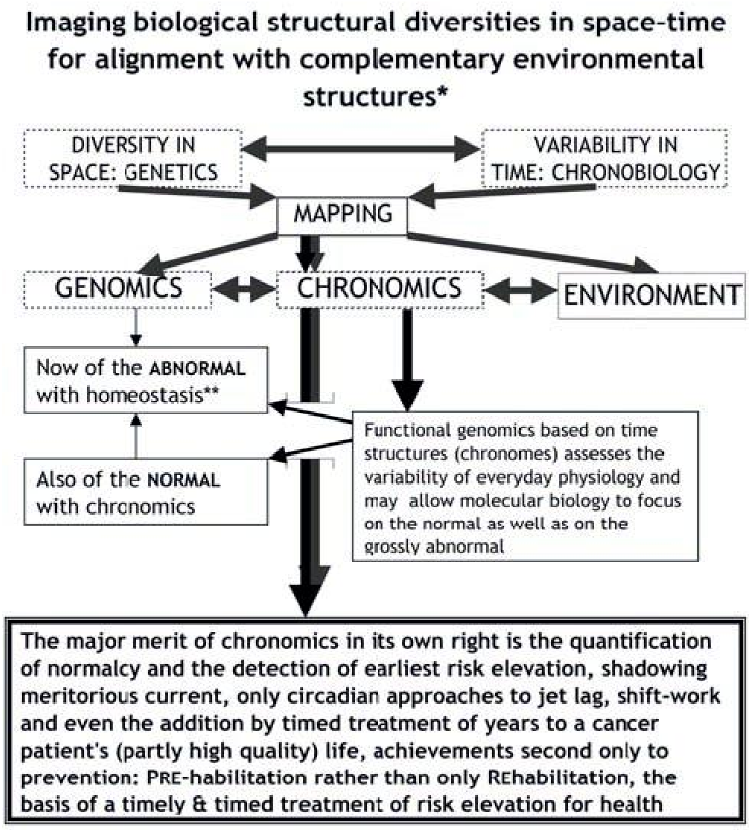


Fig. 30. Complementing genomics, chronomics - imaging in time - maps diversity integratively in time with critical results therefrom, apart from providing much improved endpoints from reductionist genome and proteome mapping in space.

for missions in extraterrestrial space, where an avoidable stroke can jeopardize a costly mission. As a spinoff from equipment designed for use in space, a chronomic crew physiological observation device is needed, for prehabilitation notably in areas of limited resources that cannot afford cardiac surgery and other procedures that are currently in use for rehabilitation.

CONCLUSION

In the introduction to his *History of the Disorders of* [the classical] *Cardiac Rhythm*, Berndt Lüderitz [238] writes: “Arrhythmias are the main complication of ischemic heart disease, and they have been directly linked to the frequently arrhythmogenic sudden death syndrome, which is now presumed to be an avoidable ‘electrical accident’ of the heart.” Conceivably, once the entire spectrum of rhythms is mapped, including yearly and perhaps trans-yearly and cis-half-yearly population rhythms, their mechanisms can be understood and can lead to countermeasures beyond current pacemaker-cardioverter-defibrillators. This remains a challenge for students of the cardiac rhythm spectrum who could clarify environmental effects near and far, so that indeed “electrical accidents” can be prevented in a rational way (Fig. 31).

To serve health, departments by that name must mandate interpretation rather than just bookkeeping for establishing imaginary “baselines” and “trends” that may be in part cycles. Almost certainly, the circadian, circannual, transannual and other

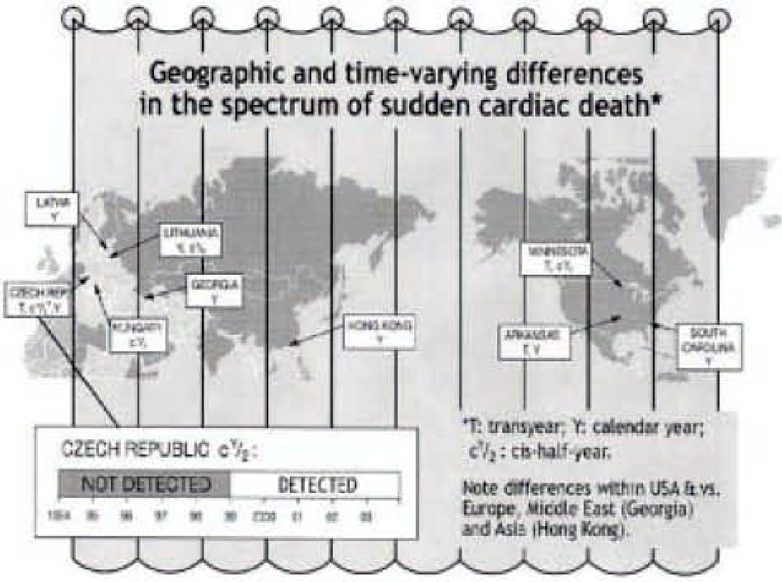


Fig. 31. A curtain of ignorance over chronoepidemiology yet to be drawn.

rhythm stages, some demonstrated to tip the scale in response to a cardiac drug, Fig. 15, and in response to daily life, Figs. 17 [238], are hints of mechanisms contributing to, if not underlying an "avoidable 'electrical accident' of the heart". Some mechanisms such as those of the heart are periodic at frequencies much lower than 1 Hz. Taking those lower frequencies into account can change the sensitivity of what we do by orders of magnitude, Fig. 32 [1, 237]. Implantable devices have already substantially lowered the incidence of SCD, and we may do even better.

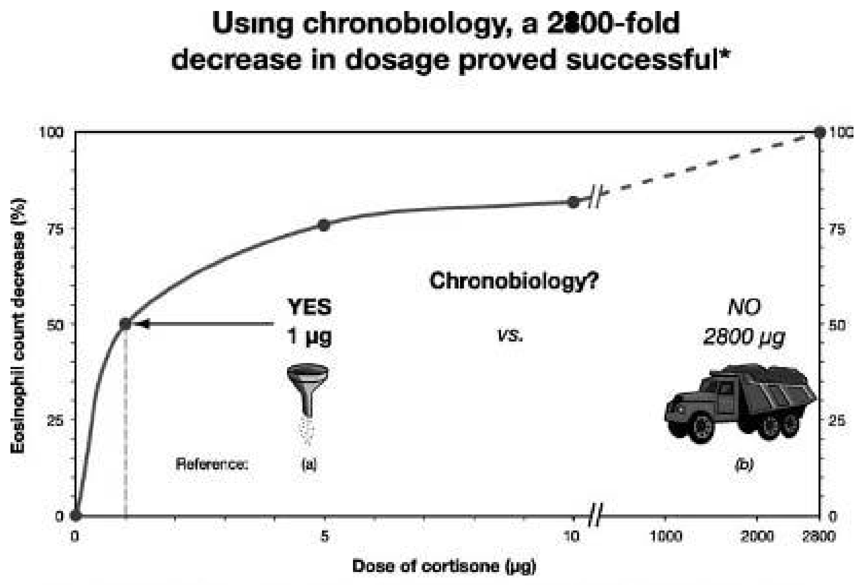


Fig. 32. A test for cortisone-line activity, based on counts of certain circulating blood cells, eliminated rhythmic changes in these cells, for 24 h. It used 2.8 mg [235]. Taking rhythms into account, results in a gain in sensitivity from a chronomic approach; cell depressing activity was detected with 1 µg of the same substance [1].

The challenges of chronobiology and chronomics are much broader [221, 222] and warrant another series of publications complementing this volume and its predecessors [196, 223, 224, 226]. As to specific applications, modern life in many settings is inconceivable without heating and cooling.

Resolution concerning chronobiology[4] and chronomics[5]

at the 2nd Int. Symp. on “Problems of rhythms in the natural sciences”, March 3, 2004

(Medical Faculty, People's Friendship University of Russia [PFUR] in Moscow)

At the March meeting, about 200 scientists, mostly from different regions of the former USSR, celebrated the 80th birthday of Professor Karl Hecht of Berlin, Germany, and the 90th birthday of Academic RAS, Professor V.E. Chain of Moscow, Russia.

The symposium's participants unanimously agreed that the study of rhythms and broader chronomes both of the cosmos and of living organisms and of their interactions has now become (in their part of the world) one of the leading biological and medical disciplines. Results of biorhythmological investigations are not only of fundamental importance, but also play an extremely important applied role. Ignoring chronomedical regularities decreases the effectiveness of treatment and may even change the direction of its positive action into an undesirable effect, such as medications given to lower blood pressure that induce overswinging (CHAT, short for circadian hyper-amplitude-tension) and thus may lead to harm. By contrast, the advocated introduction of chronomic results in practice will favorably change health care. Hence, the participants at the symposium considered it necessary to: 1) continue to systematize investigation of cosmo–biospheric interrelations; 2) publish reviews and original papers in the main journals of natural sciences and medicine; 3) systematically organize symposia and conferences in the fields of chronobiology and chronomics with special reference to chronoastrobiology; 4) organize special courses, student programs, prepare textbooks and handbooks; 5) organize special international and interdisciplinary research programs; 6) actively participate in existing projects; 7) supply mass media with information provided by specialists in these problems; 8) stress the interdisciplinary character of investigations by providing a coordinated analysis of synchronous medicobiological, chemical and geo-, helio- and cosmophysical data; 9) elaborate on the fundamental results to provide practical recommendations.

Participants at the symposium unanimously supported the practical suggestions of Professor Franz Halberg (Halberg Chronobiology Center, University of Minnesota, Minneapolis, MN, USA):

1. To introduce to the medical community, research institutions, and directly to the public, the practice of psycho-phys iologic monitoring. Cost-effective instrumentation and reference values are in use for blood pressure and heart rate assessment by centralized analyses, currently by the BIOCOS project (corne001@umn.edu): these involve comparisons of the dynamic chronomic characteristics of each time series with data from clinically healthy human peers of corresponding gender and age and are being extended to take into account geographic/geomagnetic location, ethnicity, social class and any other pertinent condition, to be sought in the person's diary, in geo- helio- and broader cosmo-physical records as well as social

conditions, to eventually be checked in the light of end-oflife outcomes. Reference values are transverse, stemming from previously monitored ‘clinically healthy’ subjects and are being complemented by longitudinal lifetime monitoring to verify health, eventually preferably from birth onwards until the end of life, preferably followed by autopsy. Current analytical programs determine, apart from a diagnosis of abnormality within the normal range of variation, also for how long the duration of monitoring has to be in a given case, starting with a 7-day record, with the duration judged by the opportunity of continuing analyses, notably after the start of therapy.

It is desirable for immediate health care and indispensable for science that some dedicated individuals (volunteers) perform monitoring during the entire lifespan or at least from the time they volunteer to life's end, starting with blood pressure and heart rate. Recent discoveries such as those of transyearly spectral components, beating it a spectral component with a period of a year (reinforcing and then canceling each other), have thus become possible.

2. The ongoing monitoring of the cosmos has to be thusaccompanied by the monitoring of the biosphere: systematic monitoring in real time of the environment on earth and in the cosmos has to be integrated with the monitoring of the bio-, noo- and ethospheres, i.e. of living matter, of the mind and of spirituality. This monitoring deserves high priority and requires obligatory governmental support.

For analyses of the monitored results it is necessary to create specialized centers, the activity of which should be directed not only to uncover the main time structures (regularities=chronomes), but also to serve for prognosis and prophylaxis in personal and environmental health care.

Signatures

Co-chairman, Organizing Committee, Dean of Medical Faculty, RPFU; Member, IAS: Prof. V.A. Frolov; Co-organizers: Ministry of Education, Russian Federation (RF); Russian People's Friendship University (RPFU); Russian and Azerbaijan Sections, International Academy of Sciences (IAS); Scientific program “Universities of Russia” of the Ministry of Education RF; Problem Committee “Chronobiology and chronomedicinez, Russian Academy of Medical Sciences (RAMS). Chairmen, Symposium Organizing Committee: D.P. Bilibin (Rector and Professor, RPFU, Russia); V. Kofler (President, International Council for Scientific Development IAS, Member, IAS, Professor, Austria); K. Hecht (President of the East-European section of IAS, Member, IAS, Professor, Germany). Co-chairmen, Organizing Committee: V.A. Frolov (Dean of the Medical Faculty, Member, IAS, Professor, Russia); K.V. Sudakov (Co-president of Russian section of IAS, Secretary-Academician of RAMS, Member, RAMS and IAS, Professor, Russia); E.N. Chalilov (Co-president, Chairmen of the Bureau of the Presidium of Azerbaijan section of IAS, Professor, Azerbaijan). Deputy chairmen: O.S. Glazachev (General Secretary of Russian section of IAS, Member, IAS, Professor, Russia); C.M. Chibisov (Member, Russian section of IAS, Professor, Russia); A.M. Mamedov (Co-president of Azerbaijan section of IAS, Member, IAS, Professor, Azerbaijan). the organizing committee included distinguished Russian and foreign scientists: RAMS members: F.I. Komarov, V.P.Kaznacheev, H.A. Agadzhanjan, V.G. Zilov, Y.A. Romanov, T.T. Berezov, V.A. Matjukhin; Professors F. Halberg (USA), G. Cornélissen (USA), S.D. Duda (Germany), K. Otsuka (Japan), G. Yamanaka (Japan), B.M. Vladimirsky (Ukraine), I.V. Radysh, A.G. Gamburtsev, R.M. Baevsky, E.S. Shnol, T.K. Breus, R.M. Zaslavskaya, S.I. Rapoport, V.V. Kassandrov and others.

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