Beyond a Spotcheck-Based Health Care: Thank You, Ram Bahadur Singh

Franz Halberg[1,*], Germaine Cornélissen[1], Jerzy Czaplicki[2], Dewayne Hillman[1], Mary Sampson[1], Othild Schwartzkopff[1] and Yoshihiko Watanabe[3]

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

[2]*Institute of Pharmacology and Structural Biology, CNRS UMR 5089, Toulouse, France*

[3]*Department of Medicine, Tokyo Women's Medical University, Medical Center East, Arakawa-ku, Tokyo, Japan*

Dr. Fabien DeMeester opens this issue with a statement in well-deserved praise of Prof. Ram Bahadur Singh. With Dr. Singh's bio- and bibliography, Dr. DeMeester covers contributions to cardiology, nutrition and life-style. He then singles out cholesterol and the omega 6:3 ratio of unsaturated fatty acids to warn, in harmony with Dr. Singh's view, that current diets represent a trend toward what may be called involution, rather than evolution. Dr. DeMeester thereafter notes the need for a reversal of this trend (and has just implemented a pilot study toward this goal). This updating and concluding note expresses thanks to both Dr. Singh and Dr. DeMeester.

We appreciate that they have both embraced a not-so-popular set of fields: chronobiology, the study of time structures, including cycles in biomedicine, and chronomics, investigating time structures, or chronomes, outside us, for interactions with chronomes in us. In medicine and in physics, the status quo is still the same as the one eloquently described in 1857 by M.J. Johnson, president of the Royal Astronomical Society, when he presented the society's medal to Samuel Heinrich Schwabe, for observations on the periodicity of sunspots [1]. He cited a number of investigators in his address for their attitude toward (sunspot) cycles, resembling the views and activities of the vast majority of scholars interested in heart health and good nutrition interpreted based on single samples or records covering at most a few days around the clock. Citing Johnson:

From Cassini II in Elem. d'Astron. 1740, vol. i, p. 82: "It is manifest because we came to report that there is no certain rule for their [i.e., sunspots'] formation, nor for their shape."

Le Monnier in 1746 (Instit. Astron., p. 83), notes: "It appears that their [sunspots'] appearance does not follow any rule."

From Long in 1764 (Astron. vol. ii, p. 472): "Solar spots observe no regularity in their shape, magnitude, number, or in the time of their appearance or continuance."

From Lalande in 1771 (Astron., vol. iii, 3131, 2d edit.): "The appearance of solar spots has no regularity."

"And Delambre's opinion may be inferred from a well-known passage in the third volume of his Astronomy (p. 20), published in 1814, where treating of the solar spots he says, 'Il est vrai qu'elles sont plus curieuses que vraiment utiles' ['They are indeed odd rather than truly useful']."

All these negative comments are likely to be (mis)applied to periods in our circulation mimicking those of sunspots. This intellectual atmosphere indeed characterizes medicine and physics in 2011, computers and satellites notwithstanding. It is the more satisfying that Prof. Singh and Dr. DeMeester have joined BIOCOS, an inquiry into the effect upon the BIOsphere of the COSmos, with respect to societal as well as individual health in particular. BIOCOS attempts to implement what Sir Norman Lockyer [2], co-discoverer of helium in the solar atmosphere and founder of the journal Nature, suggested: "Surely in Meteorology, as in Astronomy [we add: in nutrition and heart health], the thing to hunt down is a cycle, and if that is not to be found in the temperate zone, then go to the frigid zones or to the torrid zone [we add: and to Moradabad, India, and Gliwice, Poland] to look for it, and if found, then above all things, and in whatever manner, lay hold of, study it, record it and see what it means." If we abide by Sir Norman's advocacy, we cannot limit our working to "regular hours", but as a return all our work becomes sheer fun.

What is otherwise missed in the not so inferentially statistically inclined world of health care's current setting (that pays lip service to P-values for research but does not compute uncertainties in everyday clinical practice) is the aeolian nature of the dynamics (read cycles) in and around us and the need to estimate them with their uncertainties by an approach which, on the one hand, is global both in terms of time as well as in space, insofar as it rests on all of the longest pertinent time series available at a given specified moment from different geographic locations. On the other hand, it is local, again in both time and space, not only with respect to a specific geographic setting but also as to sections from different times of the same data series from the same and from different spatial settings, Table **1** and Fig. (**1**), a point critical to scholars in body-mind matters relating to individuals' and societies' health.

As another example for the need of temporally glocal analyses, there is the case of a patient, JF, desynchronized from

*Address correspondence to this author at the University of Minnesota, Minneapolis, MN 55455, USA; Tel: 612-624-6976; Fax: 612-624-9989; E-mails: halbe001@umn.edu, corne001@umn.edu

1876-3960/11 2011 Bentham Open

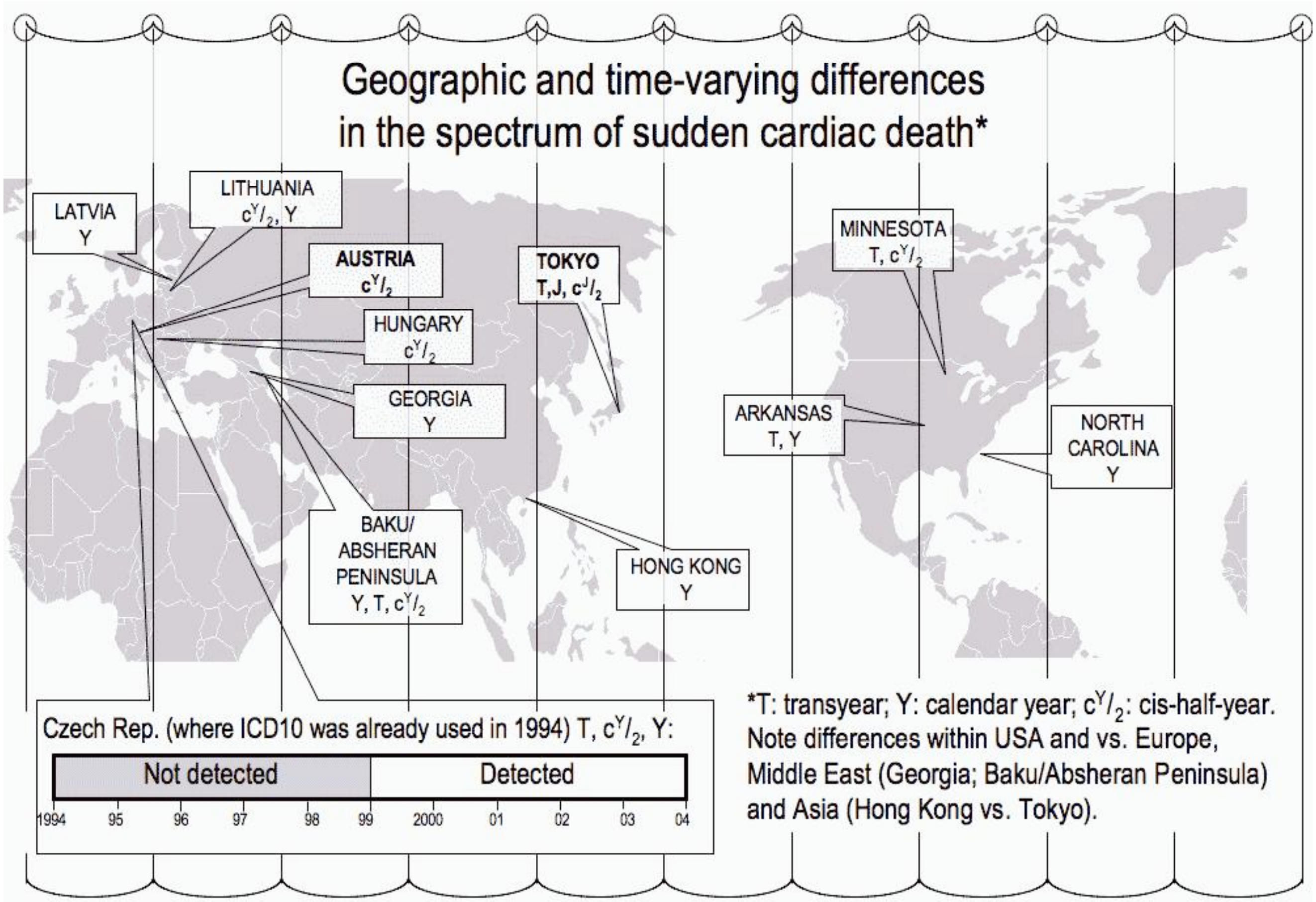


Fig. (1). A curtain of uncertainty, because of limited available data, hides any time- and geographic (geomagnetic or dip-magnetic) site-specificity of various spectral aspects of sudden cardiac death. Thus, we find a transyear in Minnesota with a cis-half-year (cY/2) and both a calendar year and a transyear in Arkansas and the Czech Republic: at the latter site a cis-half-year, corresponding in length to an also-transient period of hard solar flares (6), is detected after but not before 1999. A spectral component of the length of a calendar year is found in the incidence pattern of sudden cardiac death in North Carolina (USA), Latvia, Hong Kong and the Republic of Georgia during the available similar time spans investigated. © Halberg.

the societal 24-hour routine and thereafter resynchronized by the same routine, as shown originally for 5 (and now documented but not shown for all 6) hormones investigated during an episode of half-yearly recurring depression as well as thereafter, Figs. (**2A** and **2B**). A temporo-spatial glocal imaging (in time with its uncertainties) is desirable for each of the periodic spectral components resolved in and around us, along with any geographic difference in the temporal behaviors, if we wish to consistently assess factors or energies that influence human affairs. Moreover, all our inferences hold only for the method we used for obtaining them. When we use more sensitive methods, in JF, the case studied, instead of free-running from society's schedules, as seen in Figs. (**2A** and **2B**), we find repeated evidence for a pull by the moon as a double tidal period in a number of variables. When Prof. Germaine Cornelissen and Prof. Jerzy Czaplicki, a colleague from Toulouse, use yet more sensitive methods, they find that both society, adopting the sun's 24-hour schedule and the moon with its double tidal period of 24.8 hours, may act all the time, competing with each other in the circadian realm with more than two peaks, (Fig. **3A**-**C**) (cf. Fig. **3D**).

Once we think of time and periods in terms of statistical significance, we may wish to realize that in some geographic locations for some time spans, a number of unseen periods forms a mirror image of a spectrum of relatively novel as well as well-known nonphotic frequencies of the cosmos, notably the sun and its wind, Fig. (**4**) -- far beyond, albeit including the ~11-year Horrebow-Schwabe sunspot cycle, and/or Hale's ~22-year bipolarity cycle or the transtridecadal BEL, some of them also found in us, as seen for the Horrebow-Schwabe cycle in an elderly man's systolic blood pressure during 23 years, Fig. (**5**).

For a few years, an unseen ~16-month transyear (trans = beyond [the 1-year length]) can transiently replace the seasons in the spectrum of the incidence pattern of sudden cardiac death, not only in Tokyo but also in Minnesota, with its harsh seasons, but not in other locations, Table **1**. For instance, the observation that the same condition, the incidence pattern of sudden cardiac death during the same span of calendar time, may exhibit a far-transyear as different as ~1.3 vs. 1.7 years in populations in different geographic locations, Table **1**, is in keeping with drastic changes seen in the same population or individual with time,

Table 1. Geomagnetic/Geographic Differences among Cycles with Periods in the Range of 0.8-2.0 Years, Characterizing the Incidence of Sudden Cardiac Death (SCD)[1]* and Myocardial Infarction (MI)

Sudden Cardiac Death (SCD)[1]								
Site	Span	T, Δt, N	SCD (N)	Period (y) (95% CI)		Amplitude (95% CI)	A (% MESOR)	P-value[2]
				- - - - - Transyear (TY) or Candidate Transyear (cTY) Detected - - - - -				
Minnesota	1999-2003	5y, 1d, 1826	343	1.392 (TY)	(1.173, 1.611)	0.042 (0.00, 0.09)	22.0	0.014
Arkansas	1999-2003	5y, 1d, 1826	273	1.095	(0.939, 1.251)	0.032 (0.00, 0.07)	21.1	0.040
				1,686 (cTY)	(1.293, 2.071)	0.031 (0.00, 0.07)	20.7	0.044
Czech Rep.	1999-2003	5y, 1d, 1826	1006	0.974	(0.856, 1.091)	0.078 (0.00, 0.16)	14.2	0.007
				1.759 (cTY)	(1.408, 2.110)	0.077 (0.00, 0.15)	13.9	0.01
	1994-2003	10y, 1d, 3652	1792	1.726 (TY)	(1.605, 1.848)	0.074 (0.02, 0.13)	15.1	<0.001
				1	(0.944, 1.056)	0.052 (0.00, 0.10)	10.6	0.01
				- - - - - Candidate Transyear Not Detected - - - - -				
North Carolina	1999-2003	5y, 1d, 1826	752	0.929	(0.834, 1.023)	0.069 (0.00, 0.14)	16.9	0.007
Tbilisi, Georgia	Nov 99-2003	4.1y, 1d, 1505	130	0.988	(0.862, 1.114)	0.035 (0.00, 0.07)	40.7	0.007
Hong Kong	2001-2003	3y, 1m, 36	52	0.843	(0.651, 1.036)	(NS)	44.9	0.077
Myocardial Infarction (MI)								
Site	Span	T, Δt, N	MI (N)	Period (y)	(95% CI)	Amplitude (95% CI)	A (% MESOR)	P-value[2]
				- - - - - Coexisting Year (Circannual) and Transyear (TY) - - - - -				
Czech Rep.	1999-2003	5y, 1d, 1826	52598	1.014	(0.989, 1.038)	2.85 (2.22, 3.48)	9.88	<0.001
				1.354 (TY)	(1.252, 1.456)	1.35 (0.69, 2.02)	4.68	<0.001
	1994-2003	10y, 1d, 3652	115520	0.998	(0.988, 1.009)	3.03 (2.47, 3.60)	9.58	<0.001
				1.453 (TY)	(1.417, 1.489)	1.91 (1.34, 2.49)	6.04	<0.001
				1.15 (TY)	(1.116, 1.184)	1.23 (0.64, 1.82)	3.88	<0.001

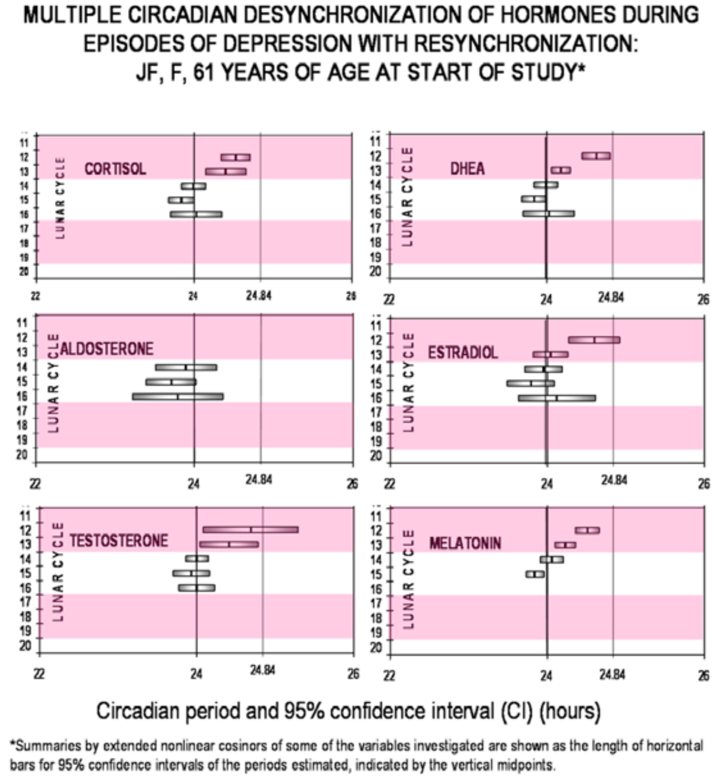
*With focus on transyears, with periods longer than 1.0 year (underlined; double underline for near-transyear).
[1]International Classification of Diseases (ICD10), Code I46.1, excluding MI and sudden death of unknown or unspecified cause (except before 1999).
T: length of data series (y=years); Δt: sampling interval (d=day, m=month); N: number of data (including 0s).
Period and 95% confidence interval (CI) estimated by nonlinear least squares. In longer (10-year) series, a near-transyear (cycle with a period between 1.0 and 1.2 years) is detected for MIs in addition to a far-transyear. Brevity of series and lack of ordering statistical significance qualify results from Hong Kong. Note that transyears are found in 3 of 6 locations ($P<0.05$ by linear least-squares) with a relative amplitude >12 (% of MESOR).
[2]From linear least-squares analyses, not corrected for multiple testing. Amplitude expressed in N/day.

in variables such as terrorism or blood pressure and heart rate, including wide drifts, for instance, between 1.3 and 1.8 years of the far-transyears. Both the drifting in the course of time and the geographic variations in the same time spans led to the postulate of a broad far-transyear (1.2 years $\leq [\tau - CI] < [\tau + CI] <$ 1.9 years, where τ is the period and CI is the 95% confidence interval of its estimation), in and around us, since a similar variability can often be found concurrently in the solar wind's speed and in earth magnetism as in physiology and epidemiology.

The late V. (Vulimiri) Ramalingaswami, a personal friend of one of us, who headed the All-India Institute for Medical Research in New Delhi, and the late B.R. (Bagepalli Ramachandrachar) Seshachar (with whose department in old Delhi FH cooperated), both former presidents of the Indian National Science Academy, both wanted to bring chronobiology to Indian medicine and science. R.B. Singh did it by dint of already summarized up to 7-day blood pressure and heart rate profiles. Should his notable finding of an association of prayer with an increased circadian amplitude of heart rate (an aspect of variability) be confirmed longitudinally rather than only by a group comparison, prayer could serve to reduce a high vascular disease risk factor, a deficient heart rate variability, findings that will have to be based on a large number of subjects and a large number of data.

R.B. and Fabien each add to BIOCOS' findings data from their settings, implementing in Moradabad or Gliwice what we achieved neither in Old and New Delhi nor in many developed areas with many more resources. It remains common practice in most research elsewhere to rely on single measurements of blood pressure or at best on 1- or 2-day profiles. R.B.'s and Fabien's investigations target routine 7-day half-hourly profiles and by computer analyses of the data, they pick up otherwise undetected variability disorders,

2A



2B

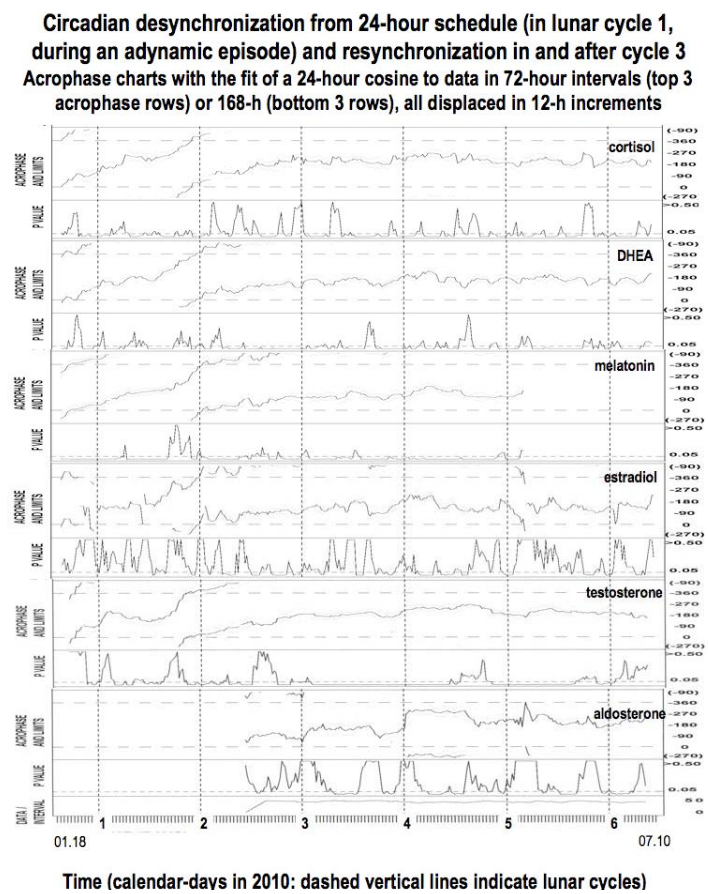
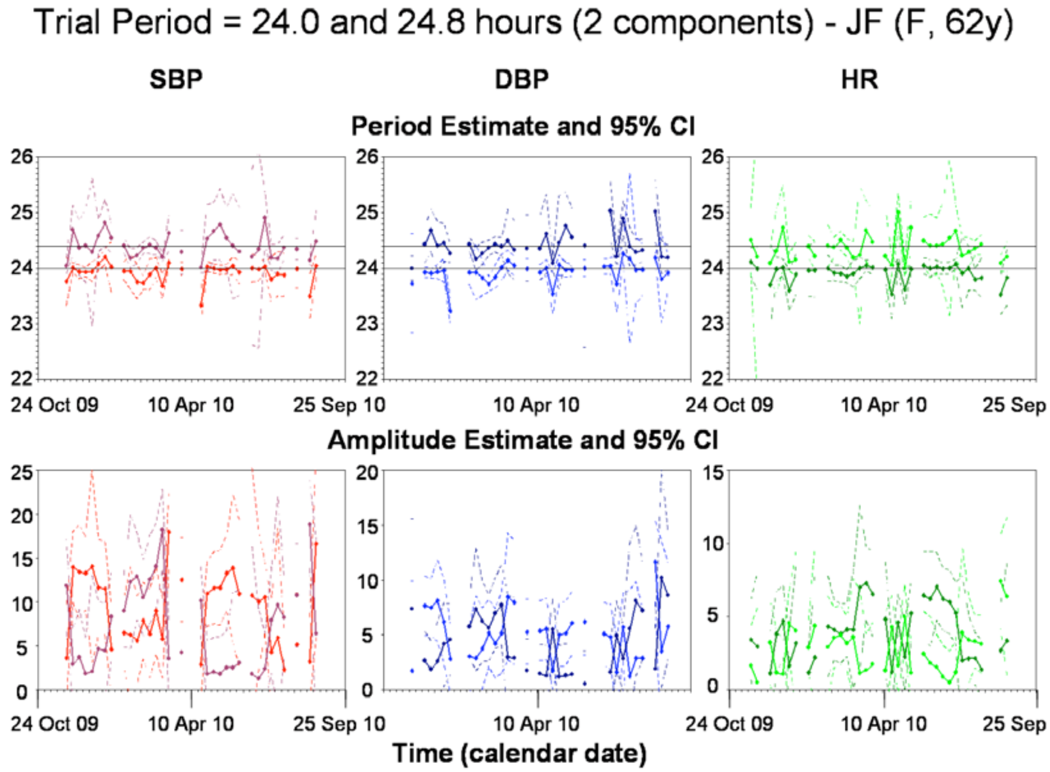
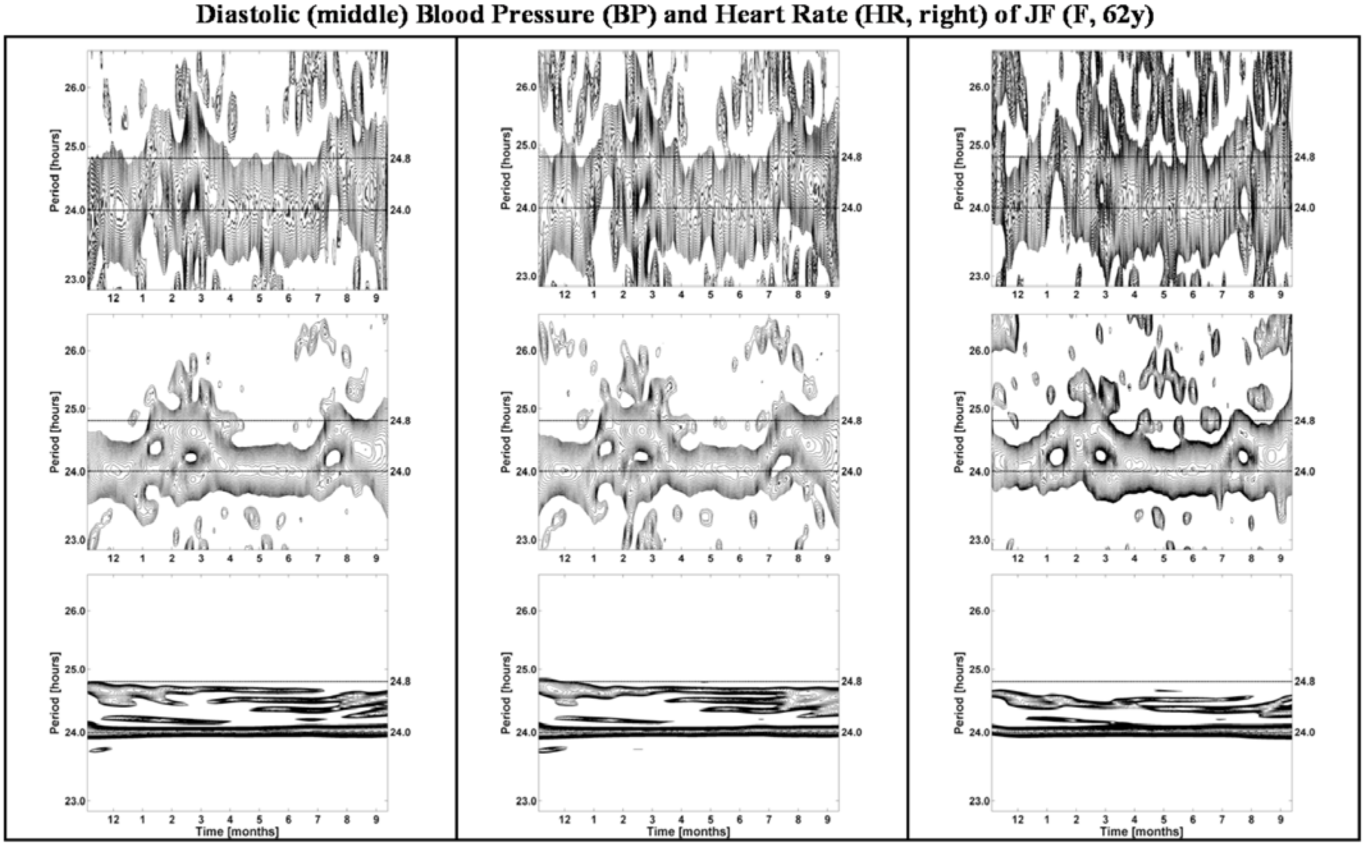


Fig. (2). (**A**) Monthly (more global) summary and (**B**) local half-weekly or weekly (more local) summary of over 5100 hormone determinations in patient JF, with half-yearly depression and adynamia recurring for 20 years suggests, at first, free-running in the light of knowledge prevailing today since 1950 [17]. Indeed, we find first only the desynchronization of a circadian endocrine system of five hormones hormones (the sixth, aldosterone, was subsequently also investigated during depression and was also found to be desynchronized; not shown). © Halberg.

3A



3B **Differential Circulatory Responses to Lunar and Solar Days: A Glocal * Analysis of Systolic (left) and Diastolic (middle) Blood Pressure (BP) and Heart Rate (HR, right) of JF (F, 62y)**

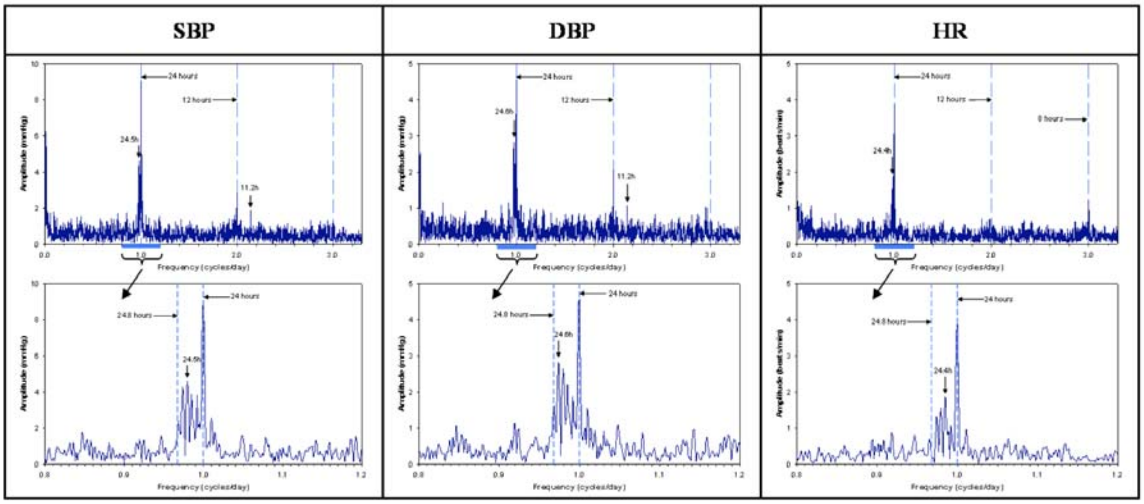


*Data (from Dec 2009 to Sep 2010) are analyzed by moving spectrograms (in Matlab), using windows of 1 (top), 2 (middle) and 10 (bottom) months. Dark bands denote high amplitude peaks, of which there are many seen in the circadian range at 1-and 2-month intervals, notably during two depressive (adynamia) episodes (2 Jan – 28 Feb and 7 Jul – 16 Sep, 2010, associated with prolongation of circadian period beyond 24.8 hours) that have been recurring twice yearly for the past 20 years. Note on the average greater pull toward 24.8 hours of BP than of HR.

Fig. 3. contd….

3C

Global view of multiple peri-circadian spectral peaks in the circulation of JF (F, 62y), gauged by systolic (S) and diastolic (D) blood pressure (BP) and heart rate (HR) *



* Data from Dec 2009 to Sep 2010 are analyzed by least squares spectra (top), revealing prominent circadian rhythm, with additional 12-hour (BP) or 8-hour (HR) harmonic term. For BP but not HR, a 11.2-hour component is also detected and validated nonlinearly. Multiple peaks in the circadian range (0.8-1.2 cycles/day zoomed from box on abscissa in top row; bottom) are observed, corresponding primarily to periods longer than 24 hours.

3D

GC (F, 60y): 3-hourly means

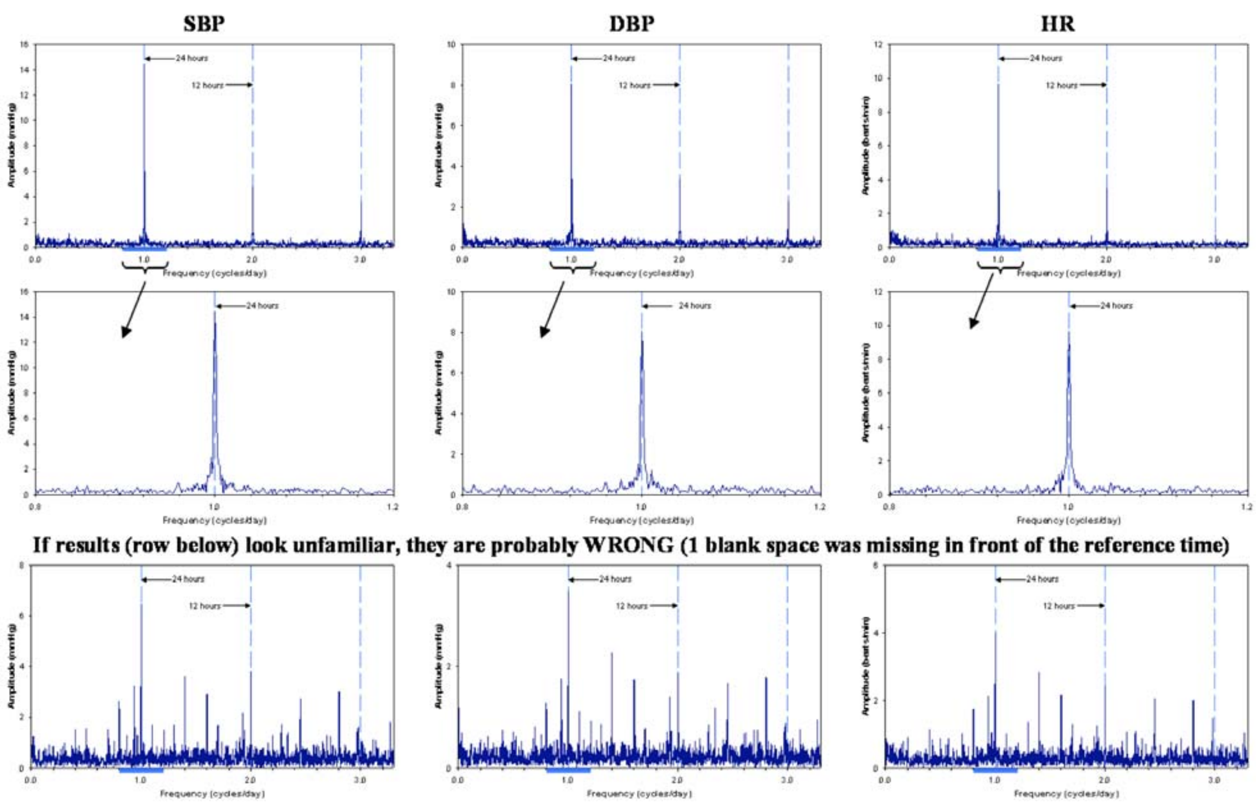


Fig. (3). In the light of information accumulating up to December 2010 [7-17], "free-running" must be interpreted as a likely ongoing competition between solar-societal and lunar days, with both leaving their mark nearly continuously. (**A**) Temporally local analysis by the concomitant nonlinear fit of trial periods of 24.0- and 24.8-hours reveals, for the majority of ~1-year vascular C-ABPM monitoring by JF, the coexistence of at least 2 time-varying periods, one likely lunar, the other representing a residual solar-societal pull. (**B**) Temporally local analysis with different magnification resolves multiple periods in JF. (**C**) Temporally global analysis confirms multiple circadian peaks, beyond sidelobes in JF. (**D**) Multiple circadian peaks are missing in a record of half-hourly measurements for the near-year span covered by GC, ~60 years, serving as both control subject and investigator, documenting, in the third row, that even **the** perfect analyst can make mistakes and is able to track down their source. © Halberg.

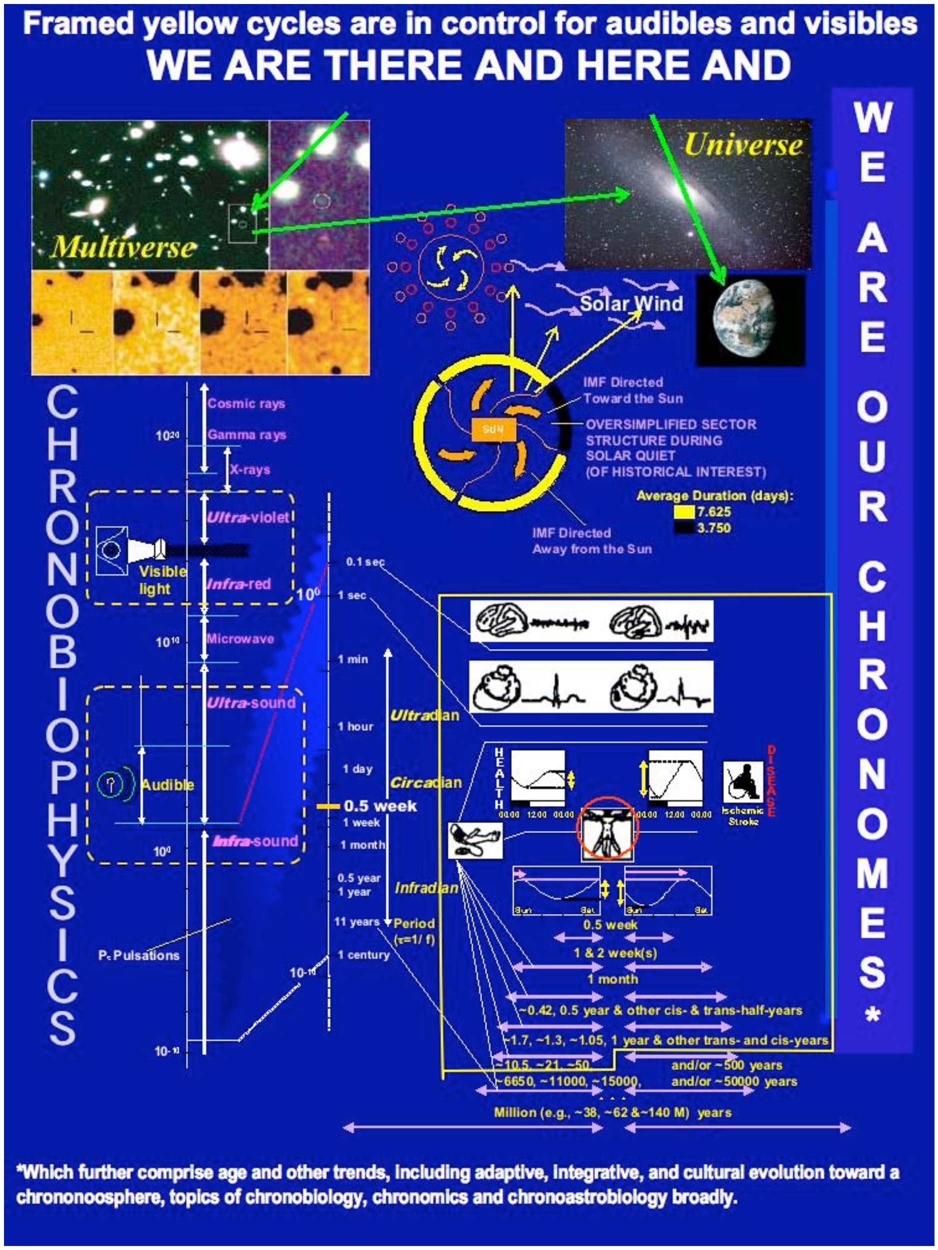


Fig. (4). The chronomes of variables in us, which came about as a function of chronomes of variables around us and were eventually coded genetically, await further exploration in health care and broader science. This transdisciplinary spectrum now includes (not shown here) the physiologically validated transtridecadal cycle of Brückner, Egeson and Lockyer [16]. This BEL and other forgotten or not yet identified cycles are pertinent in any study of mechanisms underlying adaptive, integrative and cultural evolution in the light of biological rhythms, chronobiology, and of resonances of internal with external time structures, i.e., chronomics. © Halberg.

that are not recognized by most others, not even in research, Fig. (**6**) [3-5].

As a clinician, educator, opinion-leading epidemiologist and nutritionist, with basic contributions to the role of magnesium in heart health, RB founded and presided over the International College of Cardiology, with repeated, successful meetings. Should a spotcheck "evidence"-based health care be supplanted with an automatic longitudinal self-surveillance (by its impact in the footsteps of the late Bartter in the US and the late Seshachar and the late Ramalingaswami in India), credit will go to R.B. for many things (multa) and much (multum). Carl Friedrich Gauss, the king of mathematicians and titan of science, wanted much, but not many things (multum sed non multa). Gauss wanted to be intensive, not extensive. You, R.B., please try to do the same; you bring much (chronobiologic tools and concepts) into the service of many things that are all pertinent to individual and international health, nutrition and nutriceuticals. It is hard to change the label of one kind of false positive diagnoses of high blood pressure, now "white coat hypertension", to simply "a false diagnosis based on insufficient data" and to reserve the term (true) white coat hypertension to the case when high blood pressure characterizes a physician at his hospital but not during a

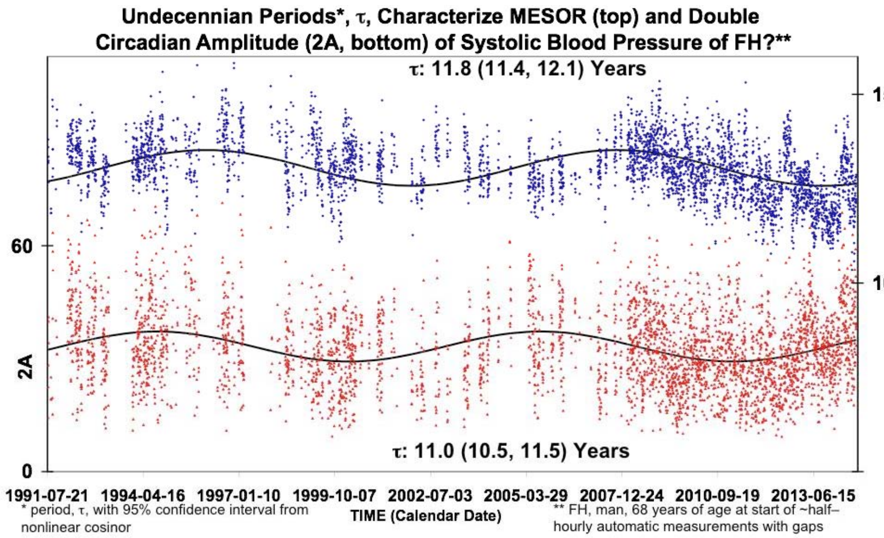


Fig. (5). Schwabe cycle in two circadian characteristics of a healthy man, i.e., in his mean (MESOR) and in the extent of daily swing (**2A**). © Halberg.

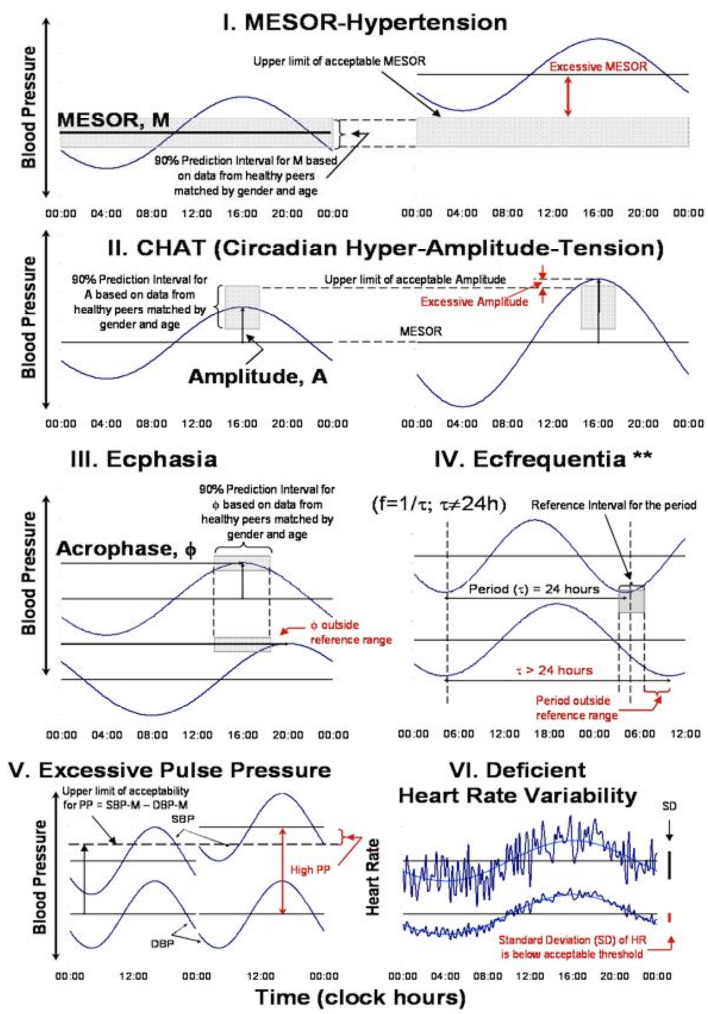


Fig. (6). Abstract visualization of vascular variability anomalies, VVAs, all to be examined chronobiologically in around-the-clock 24/7 blood pressure and heart rate surveillance, assessed as exceeding limits derived from gender- and age-matched peers for the acceptable I. MESOR (midline-estimating statistic of rhythm, usually more accurate and more precise than the arithmetic mean), II. amplitude (a measure of extent of change), III. acrophase (time of peak), IV. frequency (or reciprocal period), V. pulse pressure and VI. heart rate variability and, when these VVAs were consistently replicated in 7-day profiles, they become the corresponding vascular variability disorders, VVDs. Such coexisting VVDs constitute a vascular variability syndrome, VVS that may characterize many outliers of people, represent rates of severe cardiovascular disease greater than a high blood pressure (also a VVD!) and remain unrecognized in current practice. © Halberg.

Table 2 Comparison of 3 Vascular Profiles: 1 and 2 Based on Months of Monitoring; 3 Based on Weekends and Holidays

		Systolic Blood Pressure (mmHg)			
Span		MESOR	24h-A	24h-ϕ	(A,ϕ)
1. Jan-Aug 2008		142.6	11.76	-246	
2. Aug 08-Jan 09		140.1	13.56	-251	
3. Holiday (2008-09)		132.1	12.54	-226	
1 vs. 2 vs. 3					
	F	**32.174**	0.440	**4.598**	**2.501**
	P	**<0.001**	0.645	**0.012**	**0.045**
1 vs. 2					
	F	**4.247**	1.029	0.392	0.708
	P	**0.042**	0.313	0.533	0.495
2 vs. 3					
	F	**29.504**	0.246	**7.073**	**3.886**
	P	**<0.001**	0.621	**0.009**	**0.024**
		Diastolic Blood Pressure (mmHg)			
Span		MESOR	24h-A	24h-ϕ	(A,ϕ)
1. Jan-Aug 2008		87.3	5.94	-236	
2. Aug 08-Jan 09		86.9	8.11	-242	
3. Holiday (2008-09)		81.9	9.08	-226	
1 vs. 2 vs. 3					
	F	**13.248**	1.896	1.129	1.457
	P	**<0.001**	0.154	0.327	0.219
1 vs. 2					
	F	0.324	**5.029**	0.618	2.827
	P	0.571	**0.027**	0.434	0.065
2 vs. 3					
	F	**13.581**	0.254	1.740	0.949
	P	**0.001**	0.616	0.192	0.391
		Heart Rate (beats/min)			
Span		MESOR	24h-A	24h-ϕ	(A,ϕ)
1. Jan-Aug 2008		74.9	4.92	-246	
2. Aug 08-Jan 09		75.8	5.28	-253	
3. Holiday (2008-09)		69.6	7.95	-253	
1 vs. 2 vs. 3					
	F	**21.029**	2.543	0.146	1.355
	P	**<0.001**	0.082	0.865	0.253
1 vs. 2					
	F	0.785	0.053	0.187	0.120
	P	0.378	0.819	0.667	0.887
2 vs. 3					
	F	**37.279**	3.392	0.001	1.697
	P	**<0.001**	0.069	0.975	0.189

A: Amplitude; ϕ: Acrophase, expressed in (negative) degrees, with 360˚ ≡ 24 hours, 0˚ = 00:00. Results from parameter tests (Bingham C, Arbogast B, Cornélissen Guillaume G, Lee JK, Halberg F. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982; 9: 397-439). For this time-microscopic assessment, the data during the 4 days of vacation in span 3 were removed from span 2 prior to analysis.

vacation or during weekends, Table **2**, and not (yet) on Sundays, when he does not work. This view in the light of 23 years of around-the-clock data differs from that based on the false platinum standard of a 24-hour profile. Lessons from thousands of days of longitudinal around-the-clock data on the same person showing the development of a high blood pressure during 23 years [5] replace inferences from 1 day of monitoring on hundreds of thousands of people. Established views are hard to change. But one person may succeed: Ram Bahadur Singh, notably if Fabien DeMeester helps, as he did before and in this issue and as these authors and others try to do in their disciplines [6] and beyond [7-17].

REFERENCE

[1] Johnson MJ. Address delivered by the President, M.J. Johnson, Esq., on presenting the Medal of the Society to M. Schwabe. Mon Not R Astron Soc 1857; 17: 126-32.

[2] Lockyer N. Contributions to Solar Physics. London: Macmillan; 1874. 676 pp. "The thing to hunt down is a cycle", pp. 424-425.

[3] Halberg F, Cornélissen G, Otsuka K, *et al*. Extended consensus on need and means to detect vascular variability disorders (VVDs) and vascular variability syndromes (VVSs). World Heart J 2008; 11(14): 28.

[4] Halberg F, Cornélissen G, Cegielski N, *et al*. Circadian dysfrequentia of cortisol, melatonin, DHEA, testosterone and estradiol. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Noninvasive Methods in Cardiology, Brno, Czech Republic. Brno: Faculty of Medicine, Masaryk University. September 16-17, 2010, pp. 9-22.

[5] Watanabe Y, Cornélissen G, Halberg F, *et al*. Infradian modulation of the development of human true white-coat MESOR-hypertension. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Noninvasive Methods in Cardiology, Brno, Czech Republic. Brno: Faculty of Medicine, Masaryk University. September 16-17, 2010, pp. 104-19.

[6] Rieger E, Share GH, Forrest DJ, Kanbach G, Reppin C, Chupp EL. A 154-day periodicity in the occurrence of hard solar flares? Nature 1984; 312: 623-5.

[7] Mikulecky M. My heart, the earth, the moon and the sun. In: Mikulecky M, Ed. Sun, Moon and Living Matter. Bratislava, Slovakia. Bratislava: Slovak Medical Society; June 28-July 1, 1994. pp. 150-7.

[8] Mikulecky M, Ed. The Moon and Living Matter. Kosice, Slovakia. Bratislava: Slovak Medical Society; September 23-25, 1993. pp. 97.

[9] Mikulecky M, Ed. Sun, Moon and Living Matter. Bratislava, Slovakia. Bratislava: Slovak Medical Society; June 28-July 1, 1994. pp. 159.

[10] Mikulecky M, Ed. Chronobiology & Its Roots in the Cosmos. High Tatras, Slovakia, Bratislava: Slovak Medical Society; September 2-6, 1997. pp. 287.

[11] Otsuka K, Ed. Proceedings, 1st International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 11 Nov 2000, Tokyo, Japan. Biomed Pharmacother 2001; 55(Suppl 1): 7s-190s.

[12] Otsuka K, Ed. Proceedings, 2nd International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 17 Nov 2001, Tokyo, Japan. Biomed Pharmacother 2002; 56 (Suppl 2): 231s-382s.

[13] Otsuka K, Ed. Proceedings, 3rd International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 9 Nov 2002, Tokyo, Japan. Biomed Pharmacother 2003; 57 (Suppl 1): 1s-198s.

[14] Otsuka K, Ed. Proceedings, 4th International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 8 Nov 2003, Tokyo, Japan. Biomed Pharmacother 2004; 58 (Suppl 1): S1-S188.

[15] Otsuka K, Ed. Proceedings, 5th International Symposium Workshop on Circadian Rhythms and Clinical Chronotherapy, 6 Nov 2004, Tokyo, Japan. Biomed Pharmacother 2005; 59 (Suppl 1): S1-S261.

[16] Halberg F, Cornélissen G, Sothern RB, Czaplicki J, Schwartzkopff O. Thirty-five-year climatic cycle in heliogeophysics, psychophysiology, military politics, and economics. Izvestiya Atmos Ocean Phys 2010; 46 (7): 844-864.

[17] Halberg F, Cornélissen G, Katinas G, *et al*. Transdisciplinary unifying implications of circadian findings in the 1950s. J Circadian Rhythms 2003; 1(2): 61. www.JCircadianRhythms.com/content/pdf/1740-3391-2-3.pdf

EXPLANATORY NOTE

The studies in Figures 2 and 3 were made in the course of investigations made possible by the motivation and competence of Ms. Judy Finley, her daughter Ms. Faithe Thomas, and her granddaughter Lizbeth Thomas, carried out in cooperation with Dr. Tomoshige Kino of the Eunice Kennedy Shriver National Institute for Child Health and Human Development, National Institutes of Health, Bethesda, Maryland, USA, and Dr. George P. Chrousos of the First Department of Pediatrics, Athens University Medical School, Athens, Greece. They have been the subject of the following titles:

[1] Halberg F, Kino T, Siegelova J, *et al*. Amplitude ratios of half-weekly vs. daily variability in diastolic blood pressure in putative magnetolability: with appendix. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Proceedings, Noninvasive Methods in Cardiology, Brno, Czech Republic, July 7-10, 2009. pp. 192-207. http://web.fnusa.cz/files/kfdr2009/sbornik_2009.pdf

[2] Cornelissen G, Halberg F, Finley J, *et al*. Urinary output and geomagnetism revisited. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Noninvasive Methods in Cardiology, September 16-17, 2010, Brno, Czech Republic. Brno: Faculty of Medicine, Masaryk University. pp. 75-79.

[3] Cornelissen G, Halberg F, Guillaume F, *et al*. Grounding: Does it affect physiology? Proceedings, 15th Congress of Clinical Nutrition, El Sakhna, Egypt, September 19-22, 2010. pp. 17-18.

[4] Cornelissen G, Halberg F, Guillaume F, *et al*. Grounding or earthing: glimpses at physiology and pathology. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Noninvasive Methods in Cardiology, September 16-17, 2010, Brno, Czech Republic. Brno: Faculty of Medicine, Masaryk University. pp. 51-56.

[5] Cornelissen G, Halberg F, Hillman D, *et al*. Abstract modeling of events in a recurrent half-yearly adynamia with internal and/or external, e.g., circadian desynchronization. Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 10-11.

[6] Finley J, Halberg F, Cornelissen G, *et al*. Chronobiologically interpreted ambulatory blood pressure monitoring (C-ABPM) in every home. Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 12-13.

[7] Halberg F, Cornelissen G, Cegielski N, *et al*. Circadian dysfrequentia of cortisol, melatonin, DHEA, testosterone and estradiol. In: Halberg F, Kenner T, Fiser B, Siegelova J, Eds. Noninvasive Methods in Cardiology, September 16-17, 2010, Brno, Czech Republic. Brno: Faculty of Medicine, Masaryk University. pp. 9-22.

[8] Halberg F, Cornelissen G, Hillman D, *et al*. Variability disorder: recurrent adynamia with lengthened circadian cortisol, DHEA, blood pressure, pulse and vigor cycles. Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 14-15.

[9] Halberg F, Cornelissen G, Hillman D, *et al*. Lunar synchronization of magnetolabile grandmother sharing cis-halfyear with granddaughter in ratings of comparative general well-being. Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 16-17.

[10] Hillman D, Finley J, Halberg F, *et al*. Data during sleep are indispensable for chronobiologically interpreted ambulatory blood pressure monitoring (C-ABPM). Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 28-30.

[11] Ilyia E, McCraty R, Halberg F, *et al*. Frequency desynchronization of salivary cortisol and DHEA in a half-yearly recurrent adynamia episode. Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 18-19.

[12] Thomas F, Hillman D, Halberg F, *et al*. Chronobiologically interpreted C-ABPM in every home for 24-hour synchronized individuals. Time Series (not spotcheck) Evidence-Based Holistic Approach to Health, 1st International Workshop of the TsimTsoum Institute, Krakow, Poland, June 3, 2010, pp. 20-21.

[13] Halberg F, Cornelissen G, Grambsch P, *et al*. Personalized chronobiologic cybercare; other chronomics' progress by trans-disciplinary cycles' congruences: Season's Appreciations, 2009. J Appl Biomed 2011; 9: 1-34.

[14] Halberg F, Cornelissen G, Ilyia E, *et al*. Selenosensitivity: half-yearly recurrent adynamia and loss of adrenocortical and vascular synchronization with society. Geronto-Geriatrics: Int J Gerontol Chronome Geriatr, in press.

Received: December 21, 2010 Revised: December 22, 2010 Accepted: December 22, 2010