SCRIPTA MEDICA (BRNO) – 80 (4): 157–166, *October 2007*

CHRONOBIOLOGY OF HIGH BLOOD PRESSURE

CORNÉLISSEN G.[1], HALBERG F.[1], BAKKEN E. E.[2], WANG Z.[3], TARQUINI R.[4], PERFETTO F.[4], LAFFI G.[4], MAGGIONI C.[5], KUMAGAI Y.[6], HOMOLKA P.[7], HAVELKOVÁ A.[7], DUŠEK J.[7], SVAČINOVÁ H.[7], SIEGELOVÁ J.[7], FIŠER B.[7]

[1]Chronobiology Center, University of Minnesota, Minneapolis, Minnesota, USA
[2]North Hawaii Community Hospital Inc., Kamuela, HI, USA
[3]West China Medical Center, Sichuan University, Chengdu, China
[4]University of Florence, Florence, Italy
[5]University of Milan, Milan, Italy
[6]Kitasato University East Hospital, Sagamihara, Japan
[7] Department of Diagnostics and Rehabilitation, Faculty of Medicine, Masaryk University, Brno, Czech Republic

Received after revision October 2007

A b s t r a c t

BIOCOS, the project aimed at studying **BIO**logical systems in their **COS**mos, has obtained a great deal of expertise in the fields of blood pressure (BP) and heart rate (HR) monitoring and of marker rhythmometry for the purposes of screening, diagnosis, treatment, and prognosis. Prolonging the monitoring reduces the uncertainty in the estimation of circadian parameters; the current recommendation of BIOCOS requires monitoring for at least 7 days. The BIOCOS approach consists of a parametric and a non-parametric analysis of the data, in which the results from the individual subject are being compared with gender- and age-specified reference values in health.

Chronobiological designs can offer important new information regarding the optimization of treatment by timing its administration as a function of circadian and other rhythms.

New technological developments are needed to close the loop between the monitoring of blood pressure and the administration of antihypertensive drugs.

K e y w o r d s

High blood pressure, 7-day ambulatory blood pressure monitoring, Chronobiological approach

INTRODUCTION

There is a growing body of evidence suggesting that time structures in us and around us are intricately interwoven. Most if not all components of variation found in biota are also found in the environment, and vice versa (*1*). For instance, about daily changes are seen in almost every biological variable under 24-hour synchronized conditions. It has also long been known that the phase of circadian rhythms can be manipulated by changing the phase of the environmental cycles (*2*). At least for the case of circadian rhythms, their genetic inheritance has been demonstrated on

a molecular basis (*3, 4*), suggesting that the influence from the environment has been acquired genetically during the course of evolution.

The mapping of chronomes should benefit our understanding of human health and disease in several ways. The study of human chronomes can serve the derivation of refined reference values to better define health and to identify pre-disease, so that prophylactic interventions can be instituted as early as possible, preferably before disease sets in (*5-7*). The focus is thus put on pre-habilitation, in the hope that the need for rehabilitation will thereby be reduced (*8-10*). The study of chronomes of other organisms such as bacteria (*11-13*) is also meritorious so that actions can be taken to protect humans and other animals from possible infections, and to apply any eradicating methods at the most opportune time so as to achieve highest efficacy with least side effects. Finally, the study of time structures in the environment may help safeguard the integrity of the environment while also gaining a better understanding of the relations between biota and their environment (*14, 15*).

BIOCOS, the project aimed at studying **BIO**logical systems in their **COS**mos, has obtained a great deal of expertise in the fields of blood pressure (BP) and heart rate (HR) monitoring and of marker rhythmometry for the purposes of screening, diagnosis, treatment, and prognosis. Information gained from this work suggests a close link between mental health and cardiovascular health (*16*). Too often the argument is presented that a chronobiological approach relying on longitudinal monitoring of vital signs and on a computer-assisted analysis for an inferential statistically guided interpretation of the results is too complex and too expensive and hence cannot be generally introduced to developing countries where a cost-effective health care system is needed the most. In the following, these misconceptions are dispelled and the case is made for cardiovascular health that chronobiology offers the most promising approach to improving the quality of care at a reduced cost.

Cost benefit of longitudinal monitoring versus single samples

Several studies (*17, 18*) comparing the classification of patients based on single office measurements with that based on ambulatory monitoring for one to seven days suggest that the incidence of misdiagnosis is around 40 %, in keeping with the 48% response to placebo in the Australian Therapeutic Trial (*19,20*). A comparison of circadian characteristics from day to day in records spanning at least two days further indicates the shortcomings of monitoring limited to a single 24-hour span (*21-23*). Prolonging the monitoring from one to two days reduces the uncertainty in the estimation of circadian parameters by about 35% (*24*), whereas further information on the biological week (*25-28*) requires monitoring for at least 7 days, the current recommendation of BIOCOS for everybody at the outset (*29*). It is now

widely accepted that prognosis of target organ damage is by far superior when it is based on around-the-clock monitoring than on single office measurements (*30–32*).

There can also be large day-to-day changes in the circadian characteristics of blood pressure and heart rate in some people. The mistaken impression that the circadian variation in blood pressure and heart rate is sufficiently stable to be approximated by a single 24-hour profile stems in large part from the use of statistical methods on groups of subjects rather than focusing on the individual patient. Correlation analyses applied to large groups of subjects with a wide range of average values emphasize similarity. Statistical analyses focusing on individual differences observed from one profile to another, however, yield information more likely to help the patient in need of treatment (*21*). Several case reports document this point (*7, 33–36*). Continued monitoring is the most logical solution. Feasible today by telemetry for the lifetime of laboratory animals, it still awaits industrial developments for application in human beings.

Longitudinal monitoring does not need to be costly. The high cost of ambulatory blood pressure monitoring prevailing today stems in large part from the practice to limit the procedure to special cases. Should the recommendation to screen every citizen be embraced, the cost of monitors would drop drastically as was the case for many commodities (such as the ballpoint pen, the wristwatch, and the pocket calculator) when they became widely accessible. Serial blood pressure and heart rate data can also be obtained affordably by self-measurements, as already advocated by Janeway in 1904 (*37*). Self-measurements taken 5 to 8 times a day during waking, preferably with at least occasional nightly readings (which could be taken by a family member so as not to interrupt sleep), have been successful to help the treatment of patients with malignant hypertension (*38*). Manual measurements have also been successful to separate children with or without familial antecedents of high blood pressure and/or related cardiovascular disease and to predict outcomes (*38, 39*) by the assessment of the circadian amplitude of blood pressure interpreted in the light of reference values derived specifically for self-measurements (*24*).

Merit of a chronobiological assessment and interpretation of the data

Taking serial measurements a few times each day is important to greatly reduce the error associated with single measurements. The assessment by cosinor (*2, 40*) of the circadian amplitude and acrophase in addition to the MESOR further reduces the error term since blood pressure and heart rate are usually characterized by a circadian variation of large extent. Taking only one or two measurements a day, always at awakening and/or at bedtime, may fail to reveal abnormalities seen only at other times of the day, or abnormalities that apply only to the variability in blood pressure or heart rate.

By enlarging the monitoring to the population at large, clinically healthy individuals can provide the reference values needed to identify any abnormality that may occur within the physiological range. In view of gender differences and of changes in circadian characteristics as a function of age, reference values are best specified by gender and age, and, whenever possible, also by ethnicity. Outcome studies could further refine the reference standards by relying primarily on the data provided by low-risk subjects. Reference values are needed not only for the MESOR and for the amplitude and acrophase of the 24-hour component and all pertinent harmonic terms, but also for the interpretation of time-specified single values (*7*). Whereas the presence of a prominent circadian rhythm in blood pressure is no longer contested, this knowledge has not been applied to time-specify the reference values, so that the diagnosis does not depend on the clock hour of the clinical examination, as was demonstrated both theoretically (*34*) and clinically (*41*).

A double-barreled approach has been developed for the interpretation of blood pressure and heart rate records. It consists of a parametric and a non-parametric analysis of the data, in which the results from the individual subject are being compared with gender- and age-specified reference values in health (*7*). The reference values for parameters have led to the identification of new disease risk syndromes, such as CHAT (circadian hyper-amplitude-tension, a condition characterized by a circadian amplitude exceeding the upper 95% prediction limit), BP-ecphasia (a condition characterized by a deviant circadian acrophase of blood pressure), and DHRV (decreased heart rate variability, defined as a below-threshold standard deviation of heart rate measurements collected around the clock). Together with an excessive pulse pressure (above 60 mmHg), CHAT and DHRV can make the difference between <4% and 100% morbidity in a 6-year prospective study (*42*).

Need for international relational databases linking patterns and treatment modalities to outcomes

A systematic organization into databases of all records, preferably with regular follow-ups of the subjects who provided the records, would be invaluable to build evidence-based archives (*43*). Information could thus be gathered to determine systematically and rigorously optimal chronotherapeutic regimens and to identify pre-disease conditions in a timely fashion, so that prophylactic interventions may be instituted. In addition to the data, outcomes and pertinent clinical data could be added to the existing databases. Information from both prospective trials and from retrospective analyses could add to the current knowledge. A treatment regimen found to be superior in large clinical trials in reducing the incidence of strokes and other cardiovascular events is shown in a cross-over chronobiological pilot study to decrease the incidence of CHAT. As different treatment regimens can affect the circadian blood pressure amplitude differently (*44, 45*), some schedule may induce

iatrogenic CHAT, which in turn may increase the risk of stroke, whereas another schedule may have the opposite effect (*46*). A change in morbidity/mortality could thus be associated with changes in blood pressure and/or heart rate characteristics occurring naturally or intentionally induced by a given intervention.

An important distinction needs to be made between lessons learned from large clinical trials and their application for the individual patient. Differences and trends uncovered in studies on groups, even when each subject provides only one or a few measurements, cannot be similarly assessed in medical practice when a decision needs to be made for treating the individual patient. In order to be able to reach an informed decision for the given patient, serial rather than single data should be collected. When time series are available, it becomes possible to assess risk elevation or the response to treatment for that particular patient. Available procedures include parameter tests (*47*) and cumulative control charts *(33, 35).* The kjnd of treatment, dosing, and timing then all become amenable to optimization for the given patient. The point also needs to be made that timing should routinely be introduced as a major factor in clinical trials. Without any added cost, or rather with considerable saving, chronobiological designs can offer important new information regarding the optimization of treatment by timing its administration as a function of circadian and other rhythms. 'Larger' is not necessarily better when timing is ignored, as documented both theoretically (*48*) and clinically (*49*, *50*).

Spin-offs from organized archives of long-term records

Once databases are organized to include archives of longitudinal records from test pilots, special analyses may also serve basic science. For instance, these analyses may further the understanding of the influence of environmental factors near and far on human physiology and pathology (*1*). Cases in point include the biological week (*51, 52*), the half-year (*53*), the trans-year (*54, 55*), and circadecadal and circamultidecadal cycles (*1, 56*), notably an about 10.5-year cycle in mortality from myocardial infarctions in Minnesota (*57*). In particular, the recent detection of an about 1.3-year change in blood pressure and heart rate resembling the about 1.3-year variation in the velocity of the solar wind illustrates the fact that organisms are influenced by non-photic as well as photic effects from the sun (*54, 55*). Problems related to the recent increase in mortality from stroke (*1, 57–60*) could also be more readily investigated, also accounting for a putative about 50-year cycle.

New technological developments

Not so many years ago, patients with diabetes used single daily injections of slow-acting insulin preparations aimed at covering 24 hours. Any adjustment in the daily dose relied on glucose tests in urine. Today, programmable insulin pumps use

fast-acting insulin and patients are encouraged to test their glucose concentrations in blood samples several times a day to achieve tighter control and thereby reduce their risk of complications. In a first attempt to closing the loop, the new Paradigm 512 insulin pump from Medtronic/MiniMed has recently been combined with the Paradigm Link blood glucose meter, the two devices communicating with each other by means of radio waves to automatically adjust the dosage of insulin delivery (*61*). In the case of blood pressure, 24-hour formulations of antihypertensive agents are still prevalent today, with the tacit implication that the need for medication remains constant from moment to moment and from one day to another. The technology needed to close the loop between the monitoring of blood pressure and the administration of antihypertensive drugs, however, should not differ too much from the technology already in use for the treatment of diabetes.

For a wider acceptance of the monitoring of blood pressure, new approaches may have to be considered. One possibility is the use of minimally invasive devices relying on an implanted sensor to measure blood pressure beat to beat. Another area of rapid development relates to the use of electronic textiles (*62*). Shirts are being designed to monitor a patient's vital signs and alert a doctor by means of a wireless signal at the first sign of trouble. Medical textiles incorporate current-carrying fibers into fabrics to power electronic sensors that can monitor the wearer's breathing, temperature and heart rate, and may soon be capable of monitoring also oxygen and blood glucose concentrations. The clothing thus becomes the monitoring device, whereas software controls the communications inside the on-fabric network and can send radio signals using Bluetooth or any other IEEE 802.11 wireless standard to personal computers and over the Internet (*63*). This technology offers diverse applications among which the prevention of sudden infant death syndrome (SIDS) is already within reach.

Concluding remarks

Optimization in manufacturing and marketing relies on monitoring, analysis, and outcome studies. Similar systems are in place for tracking infections, as we recently witnessed in the case of SARS (*64*). But this is not yet the case for personal health, the most precious commodity of all. It may be high time to remedy the situation, notably since all ingredients for doing so are available, namely the monitoring devices, the analytical procedures, treatment modalities and ways to optimizing their scheduling of administration, and also drug delivery devices (*65*). Closing the loop has started for diseases such as diabetes (insulin pump linked to glucose sensor) (*61*), for certain cardiovascular conditions (pacemaker-cardioverter-defibrillators), but not yet for blood pressure disorders that place a patient at a higher risk of cardiovascular disease before there is overt disease.

Blood pressure can be as variable as blood sugar. Rather than focusing on 24-hour formulations (one size fits all), tighter control may perhaps be achieved using first a radically different strategy relying on faster acting antihypertensives that can be titrated as needed not only in response to blood pressure measurements recorded automatically and continuously but also in anticipation of the usual daily, weekly, and even longer (e.g., circannual) patterns known to characterize blood pressure, including an increase prior to awakening, in preparation of the next day's activities (*66*). Whereas this may not happen overnight, we should not wait until tomorrow to use the technology that is available today. Education in chronobiology literacy at all ages can go a long way at an affordable cost, a small investment with potential great reward if by pre-habilitation the very high cost of after-the-fact care can be drastically curtailed, an approach equally applicable in developed, developing, and, where it is particularly needed, in underdeveloped countries.

A c k n o w l e d g e m e n t

Supported by US Public Health Service (GM-13981), Dr hc Dr hc Earl Bakken Fund, Ministry of Education MSM0021622402, Czech Republic.

REFERENCES

1. *Halberg F, Cornélissen G, Otsuka K, et al.,* International BIOCOS Study Group. Cross-spectrally coherent ~10.5- and 21-year biological and physical cycles, magnetic storms and myocardial infarctions. Neuroendocrinology Letters 2000; 21: 233–258.
2. *Halberg F.* Chronobiology. Annual Reviews of Physiology 1969; 31: 675–725.
3. *Pennisi E.* Multiple clocks keep time in fruit fly tissues. Science 1997; 278: 1560–1561.
4. *Plautz JD, Kaneko M, Hall JC, Kay SA.* Independent photoreceptive circadian clocks throughout *Drosophila.* Science 1997; 278: 1632–1635.
5. *Halberg F, Cornélissen G, Carandente A, Bakken E, Young E.* Chronobiologic perspectives of international health care reform for the future of children. Chronobiologia 1993; 20: 269–275.
6. *Cornélissen G, Delmore P, Bingham C, et al.* A response to the health care crisis: a 'health start' from 'womb to tomb'. Chronobiologia 1993; 20: 277–291.
7. *Cornélissen G, Otsuka K, Halberg F.* Blood pressure and heart rate chronome mapping: a complement to the human genome initiative. In: Chronocardiology and Chronomedicine: Humans in Time and Cosmos. Otsuka K, Cornélissen G, Halberg F (eds.), Life Sciences Publishing: Tokyo, 1993: pp. 16–48.
8. *Cornélissen G, Halberg F, Schwartzkopff O, et al.* Chronomes, time structures, for chronobioengineering for „a full life". Biomedical Instrumentation Technology 1999; 33: 152–187.
9. *Halberg F, Cornélissen G, Wall D, et al.* Engineering and governmental challenge: 7-day/24-hour chronobiologic blood pressure and heart rate screening: Part I. Biomedical Instrumentation Technology 2002; 36: 89–122.
10. *Halberg F, Cornélissen G, Wall D, et al.* Engineering and governmental challenge: 7-day/24-hour chronobiologic blood pressure and heart rate screening: Part II. Biomedical Instrumentation Technology 2002; 36: 183–197.
11. *Halberg F, Cornélissen G, Katinas G, Hillman D, Schwartzkopff O.* Season's Appreciations 2000: Chronomics complement, among many other fields, genomics and proteomics. Neuroendocrinology Letters 2001; 22: 53–73.
12. *Faraone P, Cornélissen G, Katinas GS, Halberg F, Siegelova J.* Astrophysical influences on sectoring in colonies of microorganisms. Scripta medica 2001; 74: 107–114.
13. *Cornélissen G, Halberg F, Gheonjian L, et al.* Schwabe's ~10.5- and Hale's ~21-year cycles in human pathology and physiology. In: Schröder W (ed.): Long- and Short-Term Variability in Sun's History and Global Change. Bremen: Science Edition, 2000: pp. 79–88.
14. *Halberg F, Wendt H, Cornélissen G, et al.* Chronobiologic monitoring of health and environmental integrity. Human Physiology 1998; 24: 728–733.

15. *Halberg F, Syutkina EV, Cornélissen G*. Chronomes render predictable the otherwise-neglected human "physiological range": position paper of BIOCOS project. Human Physiology 1998; 24: 14–21.
16. *Otsuka K, Murakami S, Kubo Y, et al.* Preface. Chronomics for chronoastrobiology with immediate spin-offs for life quality and longevity. Biomedicine and Pharmacotherapy, in press.
17. *Kumagai Y, Kuwajima I, Suzuki Y, et al*. Untenable acceptance of casual systolic/diastolic blood pressure readings below 140/90 mm Hg. Chronobiologia 1993; 20: 255–260.
18. *Schaffer E, Cornélissen G, Rhodus N, Halhuber M, Watanabe Y, Halberg* F. Outcomes of chronobiologically normotensive dental patients: a 7-year follow-up. J Amer Dental Association 2001; 132: 891–899.
19. Management Committee. Australian National Blood Pressure Study: The Australian Therapeutic Trial in Mild Hypertension. Lancet (June 14) 1980: 1261–1267.
20. *Halberg F, Cornelissen G, Halberg E, et al.* Chronobiology of human blood pressure – Medtronic Continuing Medical Education Seminars, 1988, 4th ed, 242 pp.
21. *Cornélissen G.* Instrumentation and data analysis methods needed for blood pressure monitoring in chronobiology. In: Scheving LE, Halberg F, Ehret CF (eds). Chronobiotechnology and Chronobiological Engineering. Dordrecht: Martinus Nijhoff, 1987: pp. 241–261.
22. *Tamura K, Wu J, Cornélissen G, Halberg F*. Agreement between consecutive ambulatory 24-hour blood pressure and heart rate pro les in Japanese hospital staff. Progress in Clinical and Biological Research 1990; 341A: 263–272.
23. *Watanabe Y, Cornélissen G, Halberg F, et al*. Incidence pattern and treatment of a clinical entity, overswinging or circadian hyperamplitudetension (CHAT). Scripta medica 1997; 70: 245–261.
24. *Halberg F, Scheving LE, Lucas E, et al*. Chronobiology of human blood pressure in the light of static (room-restricted) automatic monitoring. Chronobiologia 1984; 11: 217–247.
25. *Carandente F, Cornélissen G, Halberg F.* Further data and analyses. Chronobiologia 1994; 21: 311–314.
26. *Halberg F, Cornelissen G, Raab F, et al*. Automatic physiologic 7-day monitoring and chronobiology. Jap J Electrocardiology 1995; 15 (Suppl. 1): S-1-5 - S-1-11.
27. *Siegelova J, Homolka P, Dusek J, Fiser B, Cornélissen G, Halberg F.* Extracircadian-to-circadian variance transpositions early and vice versa late in life in the human circulation. Proceedings, 1st International Symposium, Workshop on Chronoastrobiology & Chronotherapy (Satellite Symposium, 7th Annual Meeting, Japanese Society for Chronobiology), Kudan, Chiyodaku, Tokyo, 11 Nov 2000, pp. 58–60.
28. *Singh RB, Cornélissen G, Siegelova J, Homolka P, Halberg F*. About half-weekly (circasemiseptan) pattern of blood pressure and heart rate in men and women of India. Scripta medica 2002; 75: 125–128.
29. *Halberg F, Smith HN, Cornélissen G, Delmore P, Schwartzkopff O*, International BIOCOS Group. Hurdles to asepsis, universal literacy, and chronobiology –all to be overcome. Neuroendocrinology Letters 2000; 21: 145–160.
30. *Mancia G, Gamba PL, Omboni S, et al*. Ambulatory blood pressure monitoring. J Hypertension (Suppl) 1996; 14: S61–S66.
31. *Mallion JM, Baguet JP, Siche JP, Tremel F, De Gaudemaris R.* Clinical value of ambulatory blood pressure monitoring. J Hypertension 1999; 17: 585–595.
32. *Mancia G, Parati G.* Ambulatory blood pressure monitoring and organ damage. Hypertension 2000; 36: 894–900.
33. *Halberg F, Cornélissen G*, International Womb-to-Tomb Chronome Initiative Group. Resolution from a meeting of the International Society for Research on Civilization Diseases and the Environment (New SIRMCE Confederation), Brussels, Belgium, March 17–18, 1995: Fairy tale or reality? Medtronic Chronobiology Seminar No. 8, April 1995, 12 pp. text, 18 gures.
34. *Cornélissen G, Halberg F.* Impeachment of casual blood pressure measurements and the xed limits for their interpretation and chronobiologic recommendations. Annals New York Academy of Sciences 1996; 783: 24–46.
35. *Cornélissen G, Halberg F, Hawkins D, Otsuka K, Henke W*. Individual assessment of antihypertensive response by self-starting cumulative sums. J Medical Engineering Technology 1997; 21: 111–120.
36. *Halberg F, Cornélissen G, Otsuka K, et al.* Chronomics detects altered vascular variabilities constituting risks greater than hypertension: with an illustrative case report. In: Mitro P, Pella D, Rybar R, Valocik G (eds). Proceedings, 2nd Congress on Cardiovascular Diseases, Kosice, Slovakia, 25–27 April 2002. Bologna: Monduzzi Editore, 2002: pp. 223–258.
37. *Janeway TC.* The clinical study of blood pressure. New York: Appleton, 1904: 300 pp.
38. *Scarpelli PT, Romano S, Livi R, et al*. Instrumentation for human blood pressure rhythm assessment by self-measurement. In: Chronobiotechnology and Chronobiological Engineering, Scheving LE, Halberg F, Ehret C. (eds). Dordrecht: Martinus Nijhoff, 1987: pp. 304–309.

39. *Halhuber MJ, Cornélissen G, Bartter FC, et al*. Circadian urinary glucocorticoid and rhythmic blood pressure coordination. Scripta medica 2002; 75: 139–144.
40. *Cornélissen G, Halberg F.* Chronomedicine. In: Encyclopedia of Biostatistics, Armitage P, Colton T (eds), v. 1, Chichester: Wiley, 1998: pp. 642–649.
41. *Bartter FC.* Periodicity and medicine. In: Scheving LE, Halberg F, Pauly JE (eds). Chronobiology. Tokyo: Igaku Shoin Ltd., 1974: pp. 6–13.
42. *Cornélissen G, Otsuka K, Chen CH-H, Halberg F*. Circadian Hyper-Amplitude-Tension (CHAT) and an elevated pulse pressure are separate cardiovascular disease risk factors. Clin Exp Hypertens, in press.
43. *Halberg F, Cornélissen G, Bakken E.* Caregiving merged with chronobiologic outcome assessment, research and education in health maintenance organizations (HMOs). Progress in Clinical and Biological Research 1990; 341B: 491–549.
44. *Tamura K, Kohno I, Saito Y, et al.* Antihypertensive individualized therapeutic strategy. Difesa Sociale 1991; 6: 109–124.
45. *Watanabe Y, Cornélissen G, Watanabe M, et al*. Effects of autogenic training and antihypertensive agents on circadian and circaseptan variation of blood pressure. Clin Exp Hypertens 2003; 25: 405–412.
46. *Shinagawa M, Kubo Y, Otsuka K, Ohkawa S, Cornélissen G, Halberg F*. Impact of circadian amplitude and chronotherapy: relevance to prevention and treatment of stroke. Biomedicine and Pharmacotherapy 2001; 55: 125–132.
47. *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.
48. *Bingham C, Cornélissen G, Halberg F*. Power of 'Phase 0' chronobiologic trials at different signal-to-noise ratios and sample sizes. Chronobiologia 1993; 20: 179–190.
49. *Halberg F, Bingham C, Cornélissen G.* Clinical trials: the larger the better? Chronobiologia 1993; 20: 193–212.
50. *Cornélissen G, Halberg F, Prikryl P, Dankova E, Siegelova J, Dusek J,* International Womb-to-Tomb Chronome Study Group. Prophylactic aspirin treatment: the merits of timing. JAMA 1991; 266: 3128–3129.
51. *Halberg F.* The week in phylogeny and ontogeny: opportunities for oncology. In vivo 1995; 9: 269–278.
52. *Cornélissen G, Engebretson M, Johnson D, et al*. The week, inherited in neonatal human twins, found also in geomagnetic pulsations in isolated Antarctica. Biomedicine and Pharmacotherapy 2001; 55 (Suppl 1): 32–50.
53. *Cornélissen G, Halberg F, Pöllmann L, et al*. Circasemiannual chronomics: half-yearly biospheric changes in their own right and as a circannual waveform. Biomedicine and Pharmacotherapy, in press.
54. *Cornélissen G, Masalov A, Halberg F, et al.* Multiple resonances among time structures, chronomes, around and in us. Is an about 1.3-year periodicity in solar wind built into the human cardiovascular chronome? Human Physiology, in press.
55. *Halberg F, Cornélissen G, Schack B*. Self-experimentation on chronomes, time structures; chronomics for health surveillance and science: also transdisciplinary civic duty? Behavioral and Brain Sciences.
56. http://www.bbsonline.org/Preprints/Roberts/Commentators?Halberg.html
57. *Halberg F, Cornélissen G, Katinas G, et al.* System times and time horizons for biospheric near-matches of primarily non-photic environmental cycles. Biomedicine and Pharmacotherapy 2002; 56 (Suppl 2): 266s-272s.
58. *Cornélissen G, Halberg F, Breus T, et al*. Non-photic solar associations of heart rate variability and myocardial infarction. J Atmospheric Solar-Terrestrial Physics 2002; 64: 707–720.
59. *Fiser B, Cornélissen G, Siegelova J, et al.* Increase in stroke deaths after 1997 in the Czech Republic. Scripta medica 2002; 75: 95–100.
60. *Johansson B, Norrving B, Lindgren A.* Increased stroke incidence in Lund-Orup, Sweden, between 1983 to 1985 and 1993 to 1995. Stroke 2000; 31: 481–486.
61. *Otsuka K* (ed). Proceedings, First International Symposium, Workshop on Chronoastrobiology and Chronotherapy (Satellite Symposium, Seventh Annual Meeting, Japanese Society for Chronobiology), Kudan, Chiyodaku, Tokyo, 11 Nov 2000.
62. *Kordella T.* A pump/meter duo. Pump and meter talk via radio waves. Diabetes Forecast. Nov 2003, p 45.
63. *Service RF*. Electronic textiles charge ahead. Science 2003; 301: 909–911.
64. *Marculescu D, Marculescu R, Park S, Jayaraman S*. Ready to ware. IEEE Spectrum. Oct 2003, pp. 28–32.

65. *Yang W.* Severe acute respiratory syndrome (SARS): infection control. Lancet 2003; 361: 1386–1387.
66. *Hrushesky JM, Langer R, Theeuwes F* (eds). Temporal control of drug delivery. Annals of the New York Academy of Sciences 618, 1991, 641 pp.
67. *Halberg F.* Some physiological and clinical aspects of 24-hour periodicity. Lancet 1953; 73: 20–32.