MEDICAL HYPOTHESES

The Derer´s biological – cosmic week and the Halberg´s circaseptan chronome

Czechoslovak academician Ladislav Derer was born 115 years ago

Mikulecky M Sr[1], Mikulecky M Jr[2]

BioCos, University of Minnesota, Minneapolis, MN, USA. **statistics@nel.edu**

Abstract: There are three common periodic intervals in the life of each human being from time immemorial: the day, the week and the year. The first one is given by the Earth´s rotation, the latter one by its revolution around the Sun. These both do have clear biomedical counterparts. The 7-day week, basically linguistically „period of change" (or a similar period, e.g. 10 days in Egypt or 8 days in Etrutria) was obviously originally considered mainly as a product of a societal agreement. Two groups of Czechoslovak clinicians-scientists, however, noted in forties of the XXth century an approximately week period in human laboratory data, after similar attempts abroad a few years earlier. In fifties, L.Dérer, respecting the mathematical and biological principles in medicine and supported by the mathematician A.Huťa, demonstrated the presence of the „6-day" rhythm in blood leukocyte counts in patients with leukemia, treated by cytostatics. Posing the question „Where is it from?", he considered also cosmic influences but was unable to study this issue more deeply due to his premature decease. Two decades later, the „Dérer´s circaseptans" found wide confirmation not only in human medicine but also in biology. The pioneering role here belongs to Franz Halberg, USA, the godfather of the „circadians" (originally „Halberg´s paranoia") since the fifties. The possible geocosmic roots of circaseptans are supposed in the geomagnetic activity from interplanetary space, generating under the influence of the Sun rotation the periods around 6–7 days. This is presently documented, surprisingly, also by analysing the Dérer´s original data using more advanced, inferentially statistical method - the Halberg cosinor regression. Thus, the optimal approximation has been achieved for the period of 6.75 days – the 4th harmonics of the Bartels solar rotation cycle. Accordingly, the week can be now, after Dérer and Halberg, understood also – same as day and year – as a biological – geocosmic phenomenon, a geomagnetic week, genetically acquired in the course of billions years´ of evolution, encoded in our chronome. The personality of Ladislav Dérer should, in the history of the Czech and Slovak biomedical sciences, be permanenly standing by such giants as the well known Jan Evangelista Purkyně („Purkinje") or as Bohumil Němec, discoverer of the mechanism of positive geotropism of plant roots *(Fig. 3, Ref. 28)*. Text in PDF *www.elis.sk.*
Key words: circaseptan, statistics, biology, cosmogeophysics, Dérer, Halberg, geomagnetic week, chronome.

Two generally known biological basic rhythms – the circadian and circaannual – are derived from the rotation of Earth and from its revolution around the Sun. Due to this geocosmic background, being present over billions of years, these two period lengths are firmly fixed in the genome (chronome) of living matter.

The third main periodic time section of human life is the week.

It, or a similar period, was appropriately sensed by people already in ancient times: as 7 days independently in China, old Peru, Babylon, Egypt, Moses´ laws; 8 days in Etruria and originally in old Rome (although called „nonus" dies, nundinae, derived from „nine") ; decades in old Greece, recently the failed experiments in French revolution (Décadries) and past Soviet Union.

The story of biomedical circaseptans starts, as pointed out by Hildebrandt (1), with the Hippocrates´, Galenus´ and Avicenna´s descriptions of the critical 7th, 14th and 21st day in the course of certain diseases. The rule of the 7th critical day in lobar pneumonia (2) disappeared not until antibiotic therapy was introduced.

Dérer anxiously reviewed the literature as to possible weekly rhythms and mentions a few citations concerning this (3). Another two older citations, along with two citations of Dérer´s papers, are given in (4). It has been hypothesized, besides other, that the approximately 7 day period was in most ancient civilizations taken from the four distinct phases of synodic Moon. Indeed, the word moon as well as month is derived from the Indoeuropean base *men- (mensis in Latin, mene and men in Greek, Mond and Monat in German, mesiac in Slovak etc.), the latter being derived from Indoeuropean *me- meaning to measure, metiri in Latin, metrein

[1]BioCos, University of Minnesota, Minneapolis, MN, USA, Department of Biometry and Statistics, Neuroendocrinology Letters, Stockholm, Sweden, and [2]Clinic of Infectology and Geographic Medicine, Medical Faculty, Comenius University, Bratislava, Slovakia

Address for correspondence: M. Mikulecky, MD, CSc, Clinic of Infectology and Geographic Medicine, Medical Faculty, Comenius University, Limbova 5, SK-833 05 Bratislava, Slovakia. Phone: +421.2.59542925

in Greek, messen in German, merať in Slovak. Thus, the Moon had always been verbatim the measure on the sky, visible to anybody. Duration of its phases could be measured in ancient times by attentive observers for synodic (new and full Moon), anomalistic (Moon size) as well as tropic (Moon height on the sky) Moon. Interestingly, the arithmetic mean of the period lengths of the 4th harmonics of the synodic, anomalistic and tropical Moon is 7.03 days. An opposite, or complementary hypothesis (5) considers a biochemical rhythm acting in human body as the stimulus for choosing the seventh day for recovery by Man. Nevertheless, according to the latter author, „the weather reveals a weekly rhythm" found in various biomedical variables. Besides, „Many weekly periodicities...are really reflections of lunar variations" (6). The 6-day rhythm was found for feeding of bed-bugs (7). A 5-6-day periodicity was observed in phosphate content of rabbit muscle, corresponding – interestingly! – to 10-meter radio-telegraphy waves (8; „kosmische Rhythmen"). An existence of „physiological week" related to ovulation and menstruation was suggested, lasting 6.5 to 9.1 days, presenting itself as its multiples and resulting in some fixed days of year ; the latter should reportedly indicate a solar effect (9). Periodic diseases, basically known since Hippocrates (1), with the 7th, 14th, 21st etc. critical days but also with other period lengths of the intervals of recurrence were described by (10, 11).

Dérer was attracted to studies of rhythms by his interest in the periodicities of hematopoiesis. Partly with collaborators, he followed the effects of cytostatics administration to leukemic patients on uricuria and blood leukocyte counts. In their first contribution (12), a few curves of blood leukocyte counts decrease are already displayed, so far without any comments, the latter being promised for a next article. Some of these hand-drawn curves, based on „interpolation" of 1 to 4 daily leukocyte counting (data not presented), show distinct waves of the period length around 6 days (Fig. 1).

In the next paper (13), three leukocyte curves together with those for uricuria and one without uricuria are shown. Five of these seven curves are accompanied by measured data. The curves were constructed, again, simply with the aid of „interpolation of the found values". All seem to display the approximately 6-day periods created by 3 to 4 peaks. It is hypothesized that the periodicity can be due to the regulative function of the central nervous system.

Similar idea, based also on the Pavlovian physiology with the cerebral cortex as the supreme master of the body, emerged (14) for explaining the striking periodicity in a 53-days´ observation of urinary excretion of three kinds of steroids, partly after ACTH injection. There were, in each of the three series, 9 to 10 more or less clear waves registered. Although they were somewhat irregular in mutual distances and amplitudes, the mean period length amounts around 5.1 to 5.6 days.

The interpretation of the found rhythmicity advanced later (15) to the general idea of *„a wider biological law"* of circaseptan reactivity, so far in blood elements as leukocytes and eosinophils, in uricuria and steroids´ urinary excretion, on impulses as cytostatics, RTG or ACTH (and Pyripher, see below). At the same time, it has been hypothesized that an impulse can only *unveil a preexisting* periodicity.

Dérer´s attempts for mathematical description of the 6-days´ periodicity

Dérer, still without possibility to use modern inferentially statistical methods, continued to search stubbornly for a better mathematical expression of the cycling. Thus, he found (16) on corresponding graphs, using sliding averages, a "virtual sinus curve of a 6-day period". He emphasized, however, that not simple but composed harmonic curves are present in the data.
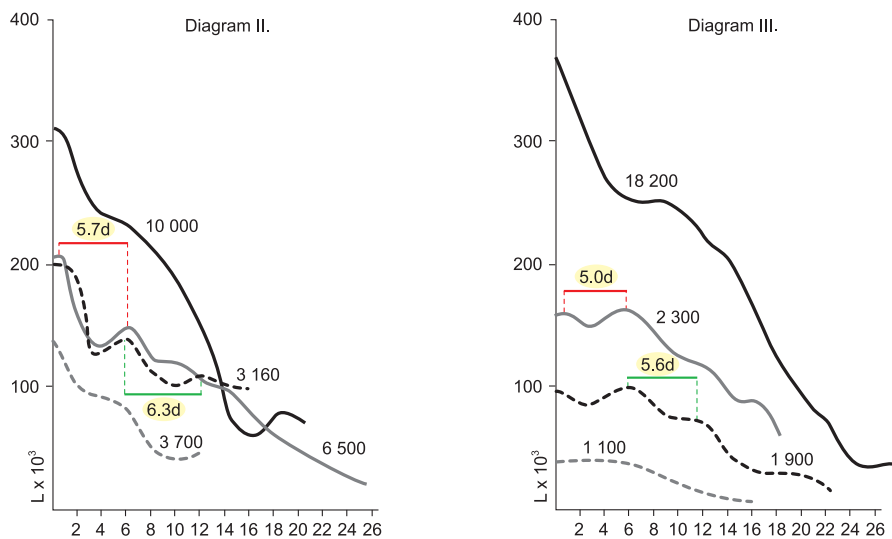

Fig. 1. Blood leukocyte counts (per cmm, in thousands, vertical axis) plotted against the time of observation (days, horizontal axis). Numbers over the curves denote milligrams of uric acid excreted by urine during the whole period of observation. This copy of Diagram II and III (12) was completed by the present authors with four period lengths in days (d), estimated from the graphs. Historically, this is the first Dérer´s authentic presentation of the „6-day" rhythm.
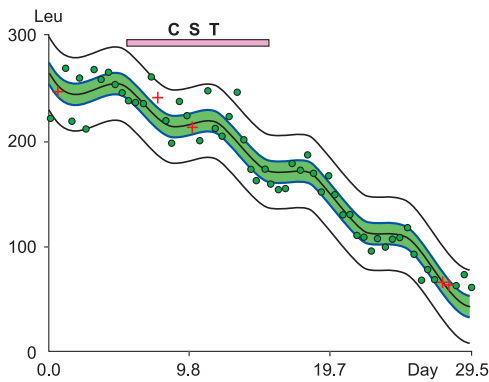
Fig. 2. Leukocyte counts (Leu, thousands per microliter) plotted against time (days) are shown as dots (data given in the original paper) with accessory 5 values (crosses) interpolated by the present authors to obtain equidistant measurements. The time interval of cytostatic therapy is shown (CST). Approximating regression function includes significant parabolic trend and significant 6.75-days period. Its 95 % confidence (narrower, for mean estimate) and 95% tolerance (wider, for one measurement from the whole population) corridors are displayed.

Calculations, based in this sense on comparing the residuals obtained by approximating separate harmonics up to 8th of the 24 hour period (3) and performed by A. Huťa, showed for neutrophil polynuclears after Pyrifer administration the dominance of statistically significant 6-day rhythm, too.

Where are circaseptans from?

Dérer, after posing this question, did not arrive at any conclusion. As said above, he believed that – despite of the manifestation of the 6-days rhythm *after* cytostatics impulse – this rhythm is *latently preexisting in the organism* (15). Interestingly, he considered also (3), in connection with the Moses order to rest the 7th day, a possibility of *cosmic origin* of this rhythm but did not see sufficient proves for that. In one of his literature overviews, he mentions (13) also the „cosmic rhythms" in man.

Dérer ´s pioneering approach confirmed and expanded by new ideas and technologies

Bibliographic analysis shows that the replies on „circaseptans" in the worldwide published papers (MEDLINE) started – with one exception (17) – in middle seventies and amount so far (1975–2009) 124 titles. In some of them (e.g. 18, 19), an allusion to Dérer is in their titles.

In Web of Science, there are so far (1986–2005) 30 relevant and positive citations of Dérer´s work listed. Thus, for example according to (20), „It is to the great credit of Ladislav Dérer..... to have emphasized the role in oncology (3) of what we now call circaseptans". An appreciation of the Dérer´s work (21) characterizes him as „the basic scientist" and „the basic biologist": „What began at Comenius University with Dérer´ s suggestion of a genetically determined circaseptan led to a model at the University of Minnesota for use by physician and biologist."

It has been shown on a eukaryotic unicell Acetabularia that week is built into this organism (22). This prominent circaseptan is resonating with the environment where it has its natural physical counterpart in geomagnetics with prominent 6.75days component. It is considered in a laboratory model of human neonatal blood pressure and heart rate circaseptans (23). In another unicell – Euglena gracilis (24) – the circaseptans are reported for pineal enzymes and melatonin. Circaseptans, as well as circadians, are „only two components among other features of ... chronome ...; it ... may represent the past as well as present cosmic effects with which early life resonated before resonance...became genetically anchored" (24). The atavistic biological week has an environmental counterpart in 6.75 day periodicity found in the planetary geomagnetic disturbance index Kp and corresponding to the 4th harmonics of the Bartels solar rotation cycle (25).

Recent recalculation of Dérer´s data arrives at a surprising result

Blood leukocyte numbers are connected with the metabolism of uric acid. This is why Dérer (3) registered, along leukocyte counts, the daily uric acid urinary excretion. It displayed a circa 6-day periodicity, too. It can be understood, besides others, roughly as the fourth harmonics of the synodic lunar cycle. It does therefore not surprise that the synodic lunar cycle periodicity had been demonstrated in the daily numbers of the gout attacks (26). Accordingly, the circaseptan, found by Dérer in leukocyte counts and interpreted by himself as a „six day" rhythm, could represent, for
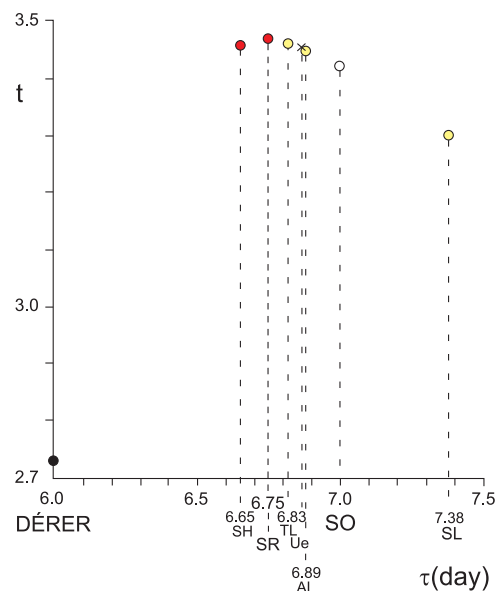

Fig. 3. The Students t-values (vertical axis) plotted as the dots against the period lengths values τ (horizontal axis) for the Dérer´s six day rhythm (6.00 days), for the master of the solar harmonic cycles (SH, 6.65 days), for the 4th harmonis of Bartels solar rotation cycle (SR, 6.75 days), for that of tropic lunar cycle (TL, 6.83 days), for the cycle suggested in (25) by Uezono et al (Ue; 6.88 days), for the 4th harmonics of anomalistic lunar cycle (AL, 6.89 days), for social week (SO, 7.00days) and for the 4th harmonics of the synodic lunar cycle (SL, 7.38 days).

example, besides others, the fourth harmonics of a cosmic roughly 28-days-cyclings as synodic (period length of the 4th harmonics is $\tau = 7.38$ days), anomalistic (6.89 days), tropical (and sideric, 6.83 days) lunar cycles. Moreover, it could be also the 4th harmonics of the Bartels rotation cycle (6.75 days) or simply the social week (7.00 days). Other possibly similar period length mentioned in the literature (17) is the „master of harmonic solar cycles" (6.65 days) . According to (25), the real period should be between 6.75 and 7.00 days – we used their arithmetical mean – 6.88 days. Finally, the simple arithmetic mean of the period lengths of the 4th harmonics of synodic, anomalistic and tropic (sideric) lunar cycles could be in the play, too – 7.03 days, i.e. almost identical with the social week: as mentioned above, ancient observers of the sky surely registered not only the periods of the synodic (new and full moon) but also anomalistic (varying Moon size) and tropical (siderical, position on ecliptics and towards stars) lunar cycle length.

In our Figure 2, the data from Dérer´s Figure 1 (1960), completed by ourselves by 5 interpolated values to obtain the equidistant time series, are shown. They were processed by Halberg cosinor regression (27) to test the presence of a parabolic trend and of one of the above mentioned period lengths τ. Each run was evaluated as to the significance of the presence of the rhythm expressed by the Student´s t-value, telling the difference of the corresponding amplitude estimate from zero in standard errors of this estimate. The significance level was set at $\alpha = 0.05$, corresponding to the critical t value of 2.0040. The resulting t values are shown in Figure 3 against the corresponding τ (period lengths) values for each run. It is obvious that the highest t-value was obtained for the period length of *6.75 days*, i.e. for the 4th harmonics of the Bartels solar rotation cycle. This, of course, does nor prove a direct causal connection between Sun and leukocytes. As a matter of fact, all tested period lengths, including the Dérers "six" days, are significantly present. For each of them, the coefficient of determination is 0.94 – 94 % of the total variance as explained by the regression. On the other hand, the peaking of the t-value precisely with the period length of 6.75 days among other used period lengths is striking and also strikingly identical with the supposed leading period here (25).

Circaseptans help to improve the therapeutic effect

A circaseptan administration schedule of immunomodulator prolongs survival of experimental animals with malignant tumour while equal daily doses of the same total drug amount shorten their life (28).

References

1. Hildebrandt G. The circaseptan reaction periodics in man. Therapeutikon 1990; 4 (7/8): 402–413.

2. Netoušek M. Internal Medicine. Textbook. Praha: Stát zdrav naklad, 1957, 1088 pp.

3. Dérer L. Rhythm and proliferation with special reference to the six day rhythm of blood leukocyte count. Neoplasma 1960; 7 (2): 117–134.

4. Levi F, Halberg F. Circaseptan (about 7 day) bioperiodicity – spontaneous and reactive – and the search for pacemakers. La Ricerca Clin Lab 1982; 12 (2): 323–370.

5. Petersen WF. Man, weather and sun. C.C.Thomas Co, Springfield, Illinois, 1947, 463 pp.

6. Kleitman N. Biological rhythms and cycles. Physiol Rev 1949; 29 (1): 1–30.

7. Mellanby K. Acta med Scand 1940; 108: 89.

8. De Rudder B. About so-called "cosmic" rhythme in man. Leipzig: Georg Thieme, 1937, 46 pp.

9. Riebold G. Sights into the periodic course of life, with special respect to the menstruation process. Stuttgart: Hippokrates Verlag, 1942.

10. Ask-Upmark E. On periodic fever. Acta Soc Med Suec 1938; 64 (5).

11. Reimann H. Periodic diseases. Medicine (Baltimore) 1951; 30: 219.

12. Dérer L, Hrubiško M, Hrúzik J. Uric acid excretion in the course of chemotherapy of leukemia. Cas Lek Ces 1949; 88 (49): 1419–1423.

13. Dérer L. About periodic effectiveness of chloralkylamine, RTG irradiation and ACTH in leukemia. Bratisl Lek Listy 1953; 33 (8): 545–553.

14. Charvát J, Kandráč M, Kopřivová A, Kuechel O. Rhythmical excretion of urinary steroids after ACTH injections. Contribution to study of the phase states in endocrinology. Cas Lek Ces 1953; 92 (48): 1314–1320.

15. Dérer L, Menkyna R, Nepelová L, Oravec D. About the rhythm provoked by cytostatics. (IInd part). Bratisl Lek Listy 1954; 34 (5): 477–484.

16. Dérer L. Concealed macroperiodicity in the reactions of the human organism. Rev Czechoslovak Med 1956; 2: 277–287.

17. Halberg F, Engeli M, Hamburger Ch, Hillman D. Spectral resolution of low frequency, small-amplitude rhythms in excreted 17-ketosteroids: probable androgen-induced circaseptan desynchronization. Acta endocrinol (Kbh) 1965; 103: 5–54.

18. Halberg F, Cornélissen G, Siegelova J, Fiser B, Dusek J, Otsuka K et al. The cosmos and CHAT, prompting blood pressure and heart rate monitoring for Derer´s week. Bratisl Lek Listy 2000; 101 (5): 260–271.

19. Halberg F. Circaseptans return to Bratislava and gather momentum beyond. Chronobiologia 18; 1991 (4): 195–202.

20. Cornélissen G, Portela A, Halberg F, Bolliet V, Falcon J. Toward a chronome of superfused pike pineals: About weekly (circaseptan) modulation of circadian melatonin release. In vivo 1995; 9: 323–330.

21. Halberg F, Marques N. Cornélisen G, Bingham Ch, Sanchez de la Pena S, Halberg J, Marques M, Jinyi W, Halberg E. Circaseptan biologic time structure reviewed in the light of contributions by Laurence K. Cutkomp and Ladislav Dérer. Acta Entomol Bohemoslov 1990; 87: 1–29.

22. Schweiger HG, Berger S, Kretschmer H, Moerler H, Halberg E, Sothern RB, Halberg F. Evidence for a circaseptan and circasemiseptan growth response to light/dark cycle shifts in nucleated and enucleated *Acetabularia* cells, respectively. Proc Natl Acad Sci USA 1986; 83: 8619–8623.

23. Katinas G, Berger S, Cornélissen G, Hillman D, Woolum JC, Engebretson M, Syutkina EV, Masalov A, Wang Zh, Wan Ch, Bakken EA, Schwartzkopff O, Halberg F. *Acetabularia acetabulum:* Unicellular model of neonatal vascular chronome. Neuroendocrinol Lett 2003; 24 (Suppl 1): 201–207.

24. Edmonds L, Balzer Y, Cornélissen G, Halberg F. Toward a chronome of Euglena gracilis (Klebs). Neuroendocrinol Lett 2003; 24 (Suppl 1): 192–199.

25. Uezono K, Halberg F, Cornélissen G, Watanabe Y, Siegelová J, Schwartzkopff O. Natural near-weeks of biology and geophysics differ from the man-made week: Transdisciplinary meta-analytic hints. Scripta Med Brno 2001; 74 (2): 92–102.

26. Mikulecký M, Rovenský J. Gout attacks and lunar cycle. Med Hypotheses 2000; 55 (1): 24–25.

27. Bingham Ch, Arbogast B, Cornélissen Germaine G et al. Inferential statistical methods for estimating and comparing cosinor parameters. Chronobiologia 1982; 9: 397–439.

28. Halberg E, Halberg F. Chronobiologic study design in everyday life, clinic and laboratory, Chronobiologia 1980; 7: 95–120.