SCRIPTA MEDICA (BRNO) – 79 (3): 135–140, *July 2006*

DIVERSITY IN TIME COMPLEMENTS DIVERSITY IN SPACE: CHRONOBIOLOGY AND CHRONOMICS COMPLEMENT MENDEL'S GENETICS AND PURKINJE'S SELF-EXPERIMENTATION

HALBERG F.[1], CORNÉLISSEN G.[1], TARQUINI R.[2], PERFETTO F.[2], SCHWARTZKOPFF O.[1], SIEGELOVÁ J.[3], FIŠER B.[3], KATINAS G. S.[1], BAKKEN E. E.[4]

[1]Halberg Chronobiology Center, University of Minnesota, Minneapolis, USA
[2]University of Florence, Florence, Italy
[3]Faculty of Medicine, Masaryk University, Brno, Czech Republic
[4]North Hawaii Community Hospital Inc., Kamuela, HI, USA

Received after revision July 2006

A b s t r a c t

A negative attitude prevailed in the late 1940s and earliest 1950s toward biological rhythms and toward what became chronobiology. Then, still in the 1950s, it turned out that these rhythms, used as „controls" of what happens, themselves can account for the difference between life and death under the seemingly standardized conditions of a laboratory, whether the stimulus was physical, like noise or whole-body irradiation; or other, such as a bacterial endotoxin or drug. A new science of the interplay of make-ups in time around and in us came about: chronobiology. Nowadays chronomics (mapping time structures) with the major aim of quantifying normalcy, thereby detecting earliest risk elevation, also yields the dividend of allowing molecular biology to focus on the normal as well as on the grossly abnormal.

K e y w o r d s

Chronobiology, Chronomics, Diversity in time, Diversity in space

INTRODUCTION

A negative attitude prevailed in the late 1940s and earliest 1950s toward biological rhythms and toward what became chronobiology. This attitude resembled that prevailing in physics in 1857, described in a series of verbatim quotes by Manuel Johnson, then president of the Royal Astronomical Society, when he awarded the society's gold medal to Heinrich Schwabe, the discoverer of the wobbly sunspot cycle, which Galileo and Newton, both owners of good telescopes, had missed.

In biology in 1949 (as now), fixing the time of day was deemed to be a sufficient precaution to "eliminate the effect of rhythms". My comparison of counts of certain circulating blood cells then involved, as controls, a 24-h synchronized group of mice

vs. one that was on the same lighting regimen, but without my realizing it immediately, it was phase-shifted by a diet restricted in calories offered in the morning, usually a time of rest for nocturnally feeding mice. I could not obtain the same results by comparisons of the same two groups when they were re-sampled at different times of day. In another case, I again compared a 24-h synchronized group with one that was phase-drifting after blinding. At different times after operation, but now at the same times of day, I had the conflicting results to be expected when one compares a 24-hour synchronized group with one that phase-drifts. The (adrenal and then pituitary and hypothalamic as well as cellular) mechanism and eventually galacto – and/or helio-geomagnetic mechanisms underlying rhythmic behavior had to be explored and ascertained before any data could be interpreted *(1,2,3)*.

CHRONOBIOLOGICAL APPROACH

Pursuit of those puzzles initiated by phase-shifts and -drifts was then labeled "paranoia". To me the results conveyed the fact that an assessment of rhythms, not only of circadians but also of changes with many other frequencies, while an important aspect of biological time measurement, pursued by others and certainly by myself, is also very much more; we are replacing imaginary baselines by the control of everyday photically and non-photically influenced physiology and eventually of everyday cosmology, for which organisms are specialized sensitive radiation detectors. Then, still in the 1950s, it turned out that these rhythms used as "controls" of what happens, themselves can account for the difference between life and death under the seemingly standardized conditions of a laboratory, whether the stimulus was physical, like noise or whole-body irradiation; or other, such as a bacterial endotoxin or drug. Any variable that I happened to sample with sufficient density for several 24-hour cycles replicated in the same individual and/or on different individuals happened to be structured in time. Often, when sampled long enough, the structure changed as a function of developmental and/or other trends, and/or was buried in noise, i.e., in patterns then unknown, often rhythms with lower frequency and eventually deterministic chaos. A new science of the interplay of make-ups in time around and in us came about: chronobiology. For the spectral element covering frequencies of 10 orders of magnitude, a biospheric-environmental spectral reciprocity and interdigitated feed-sidewards were uncovered by resolving characteristics such as periods and, for each fundamental period, corresponding amplitudes, phases and waveforms, always with the uncertainties of these estimated parameters. These characteristics in their turn became dynamic reference standards of everyday science (e.g., everyday physiology, psychology, sociology, ecology, ...). These reference standards turned out to be critical for the recognition of harbingers of a highly elevated disease risk in the usual "normal" range, and thus for the preventive treatment of earliest alterations: prehabilitation. To those who had not seen firsthand that rhythms tipped the scale between life and death in the laboratory, chronobiology as a

science at first appeared to be “unnecessary, presumptuous and inaccurate” – words never said to my face but written in a letter almost certainly not meant for publication. The issue became the disciplinary stake. It was a great pleasure when the afore-cited critic, in a major publication summarizing his life’s pursuits, requested and published a chronobiological phase chart. In this sense, he set an example for unity among those who do time-microscopy and time-macroscopy, who all contribute to transdisciplinary science based on assessment of rhythms and/or broader time structures (*4,5,6*).

With respect to science, the issue is the same as that now accepted for most published research. There is a need for inferential statistical hypothesis testing and nearly invariably for an interval as well as point estimation of characteristics. For health care, in the presence of a multifactorial statistical causality and great interindividual differences, there is the added need for an individualized inferential statistical approach in an evidence-based medicine subservient to the diagnosis of risk elevation and its treatment before (not only after) the fact of disease. The current golden standard in medical research consists of controlled clinical trials that ignore the person involved and will have to be replaced by individualized self-experimentation, to know for the given individual not only whether to pass on the salt or use the salt shaker (for an everyday example), but also whether one’s risk of severe vascular disease is low, perhaps below 4 %, or very high, nearing 100 %. In the latter case the risk should be lowered before a severe disease occurs, so that, e. g, a massive stroke is prevented.

DISCUSSION

In concerns for both a controlled transdisciplinary science and literacy in preventive health maintenance, chronobiologists can agree and benefit from unity. They will accept the biological week sooner if they actually see, in a gliding spectrum, the towering week in the human baby’s circulation, and the dominant circadian only toward the end of the first month of life. They will agree more rapidly on the importance of the biological week if they are interested in cancer prevention and find that sinusoidally increasing and then decreasing daily doses of an immunomodulator can inhibit the subsequently implanted malignant growth, whereas in equal daily doses the same total weekly dose enhances the malignant growth. Basic science will note that time-microscopy resolves what the naked eye may miss as the trans-year, a rhythm longer than the calendar year. Everybody may wish for a MESOR rather than an arithmetic average, when the former, because of a smaller standard deviation, but not the latter, allows the validation of a therapeutic effect for the given, e.g., MESOR-hypertensive person involved.

A few puzzles relating to a small fraction of my endeavors in the 1950s, which are summarized herein, with answers to a few questions, are just a small fraction of an autobiography. They are intended to help the reader to avoid the tunnel vision of

exclusive focus on circadian systems and the "bitemporal hemianopsia" of rhythms only without the realization that biological and broader science involve different interdigitated aspects of variability and that the rules of variability in time complement the rules of genetics as a biological variability in space, and insulin and penicillin are just two outcomes of homeostatic science. One time-qualified measurement is much better than none. Truisms such as a relative constancy or homeostasis have served bioscience very well for very long. They were never intended, however, to draw a curtain of ignorance over everyday physiology. In drawing these curtains, we unveil a range of dynamics resolvable in the data collection and as-one-goes analysis by computers built into smaller and smaller devices, for a continued self-surveillance of the normal and for an individualized detection of the abnormal. Chronomics (mapping time structures, *Fig. 1*) with the major aim of quantifying normalcy, thereby detecting earliest risk elevation, also yields the dividend of allowing molecular biology to focus on the normal as well as on the grossly abnormal (*5,6,7*).

Halberg F., Cornélissen G., Tarquini R., Perfetto F.,
Schwartzkopff O., Siegelová J., Fišer B., Katinas G. S., Bakken E. E.

RŮZNORODOST V ČASE DOPLŇUJE RŮZNORODOST V PROSTORU: CHRONOBIOLOGIE A CHRONOMIKA DOPLŇUJE MENDLOVU GENETIKU A PURKYŇOVY NA SOBĚ PROVÁDĚNÉ EXPERIMENTY

Souhrn

Na konci čtyřicátých a na začátku padesátých let převažovaly negativní postoje k biologickým rytmům a k tomu, co se později stalo chronobiologií. Potom, stále ještě v padesátých letech, se ukázalo, že tyto rytmy použité jako kontroly mohou samy o sobě odpovídat za rozdíl mezi životem a smrtí za zdánlivě standardizovaných podmínek v laboratoři, ať již stimulus byl fyzikální, jako hluk nebo celotělové ozáření, nebo jiný, jako bakteriální endotoxin nebo lék. Vznikla nová věda o vzájemných souvislostech dění v čase okolo nás a v nás: chronobiologie. Dnes chronomika (mapování časových struktur), jejímž hlavním cílem je kvantifikace normality a tím zjištění co nejdřívějšího zvýšení rizika, také umožňuje, aby se molekulární biologie soustředila na to, co je normální, i na to, co je výrazně abnormální.

Acknowledgement

This work was supported uS Public Health Service (gM-13981), Dr hc Dr hc Earl Bakken Fund. MSM 0021622402, MSM 0021622402

REFERENCES

1. *Halberg F.* Some physiological and clinical aspects of 24-hour periodicity. Journal-Lancet (Minneapolis) 1953; 73: 20–32.
2. *Halberg F, Stephens AN.* Susceptibility to ouabain and physiologic circadian periodicity. Proc Minn Acad Sci 1959; 27, 139–143.
3. *Halberg F.* Chronobiology. Ann Rev Physiol 1969; 31: 675–725.
4. *Halberg F.* Chronobiologie; rythmes et physiologie statistique. In: Marois M, editor. Theoretical Physics and Biology. Amsterdam: North-Holland, 1969: 347–393. Discussions pp. 339–344 and 394–411.

5. *Halberg F.* Laboratory techniques and rhythmometry. In: Mills JN, editor. Biological Aspects of Circadian Rhythms. London/New York: Plenum Press, 1973. p. 1–26.
6. *Halberg F, Cornélissen G, Katinas G, Syutkina EV, Sothern RB, Zaslavskaya R, Halberg Francine, Watanabe Y, Schwartzkopff O, Otsuka K, Tarquini R, Perfetto F, Siegelova J.* Transdisciplinary unifying implications of circadian findings in the 1950s. J Circadian Rhythms 2003; 1: 2. 61 pp. www.JCircadianRhythms.com/content/pdf/1740-3391/1/2.pdf
7. *Halberg F, Cornélissen G, Regal P, Otsuka K, Wang ZR, Katinas GS, Siegelova J, Homolka P,Prikryl P, Chibisov SM, Holley DC, Wendt HW, Bingham C, Palm SL, Sonkowsky RP, Sothern RB, Pales E, Mikulecky M, Tarquini R, Perfetto F, Salti R, Maggioni C, Jozsa R, Konradov AA, Kharlitskaya EV, Revilla M, Wan CM, Herold M, Syutkina EV, Masalov AV, Faraone P, Singh RB, Singh RK, Kumar A, Singh R, Sundaram S, Sarabandi T, Pantaleoni GC, Watanabe Y, Kumagai Y, Gubin D, Uezono K, Olah A, Borer K, Kanabrocki EA, Bathina S, Haus E, Hillman* D, *Schwartzkopff O, Bakken EE, Zeman M*. Chronoastrobiology: proposal, nine conferences, heliogeomagnetics, transyears, near-weeks, near-decades, phylogenetic and ontogenetic memories. Biomed Pharmacother 2004; 58, Suppl.1, pp. 170–186.

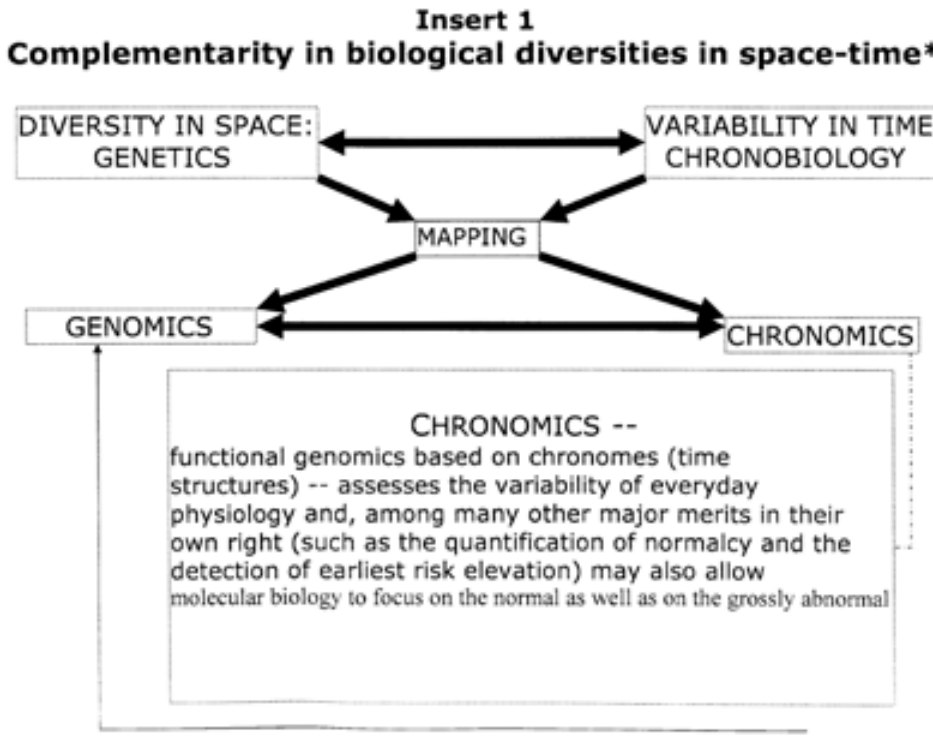

Fig. 1
Complementarity in biological diversities in space-time