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FROM TIME-UNSPECIFIED MEASUREMENTS TO CHRONOBIOLOGICAL SPECIALTIES SUCH AS CHRONOMEDICINE AND CHRONOASTROBIOLOGY: CHALLENGES FOR MANUFACTURING

HALBERG F.[1], CORNÉLISSEN G.[1],. WATANABE Y.[2], SIEGELOVÁ J.[3], FIŠER B.[3]

[1] Chronobiological Laboratories, University of Minnesota, Minneapolis, MN, USA
[2] Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan
[3] Department Functional Diagnostics and Rehabilitation, Faculty of Medicine, Masaryk University, Brno

A b s t r a c t

The past half-century has provided the designs implemented first by self-measurements and desk computations and eventually the automatic methods. Biotelemetry for humans is now available on the one hand with more and more sophisticated pacemakers, cardioverters and defibrillators as well as drug pumps on the therapeutic side. Among diagnostic devices, there are implanted heart rate monitors and more ambitious hemodynamic analyzers that record, with heart rate, also blood pressure, albeit as yet only on the right side of the circulation. The tasks on hand are, first, to improve the diagnostic devices to the point where they detect the earliest risk elevation rather than only overt disease; second, to render the therapeutic devices capable of preventive treatment and, third, to close the loop between the aforementioned devices to render preventive treatment automatic or at least self-implementable by the subject concerned.

K e y w o r d s

chrobiology, chronomedicine, chronobioastronomy, Halberg cosinor analysis

A b b r e v i a t i o n s

MESOR midline - estimating statistic of rhythm, 2A - double amplitude (measure of the extent of predictable change within a cycle), CHAT - circadian hyperamplitude tension of blood pressure

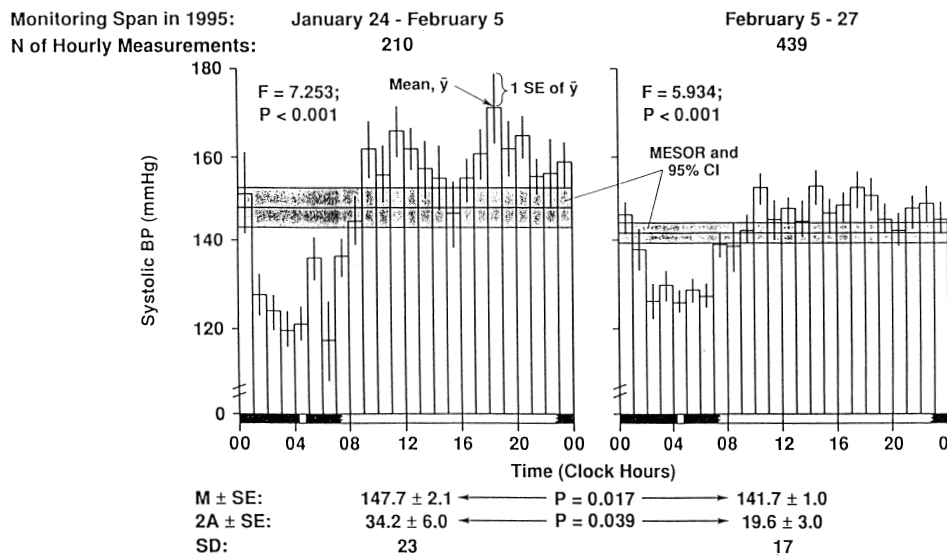
INTRODUCTION

At any science fair in Brno, the home city of Johann Gregor Mendel, best known as the founder of genetics, biotechnology should be in the foreground. Chronobiologic data revealing that the same dose of the same hormone can stimulate or inhibit DNA synthesis, in a rhythmically changing sequence (*1*), suggest that chronobiotechnology is more than a play on words. It is not generally known that in fact Mendel published more on meteorology than on plant hybridization. By providing a living example for monitoring the environment, the time structures of which are now coded in our genes, Mendel laid the groundwork for chronoastrobiology.

Brno was also the home of *Kurt Gödel*, the mathematician who provided notes of healthy caution, e.g., for those who work on software to analyze the results of the automatic monitoring of blood pressure, started in Brno by *Jan Peňáz* and brought to the clinic by the team of *Jarmila Siegelová, Bohumil Fišer* and *Ivan Duris*. These investigators pioneered blood pressure chronotherapy guided by a longitudinal analysis with an individualized control chart (*2*), with drugs by the local pharmaceutical manufacturer Lachema (*Fig.1*). Against this background, we open a competitive exhibition of wares at a gathering of buyers and sellers in Brno in 1998, to acquaint the public at large, these most numerous prospective buyers with the range and quality not only of currently available products, but also with what can be done for fairs to come that meet everybody's needs for their health care.

Chronomedicine

The current disease-cure-oriented health care system does too little too late, at too great an expense for those few who can afford it. Engineering for concomitantly resolving the external conditions and the internal schedules—chronoengineering in the broad sense, in the service of a project on the Biosphere and the Cosmos (*3*, *4*) – could change this status quo. It could thus create a system that recognizes early any elevation of the risk generated by the environment and/or the organism, blows



*** 240 mg Diltiazem HCl taken daily by 75-year-old man (FH) after getting up (left) or during an interruption of sleep (right).**

Fig. 1
Individualised blood pressure (BP) chronotherapy
Lower circadian double amplitude (2A) and MESOR (M) after switching treatment time from 08.30 (left) to 04:30 (right)*

a whistle as a minimum, and acts automatically by instituting countermeasures as an optimum. Chronobioengineering for contemporaneous external as well as internal monitoring and decision-helping would yield new individualized information from the resolution of predictable variations that occur within the physiologic range, the chronomes, i.e., genetically anchored multifrequency rhythms, chaos and trends in both rhythmic and chaotic variation.

METHODS

Their resolution by chronobiometry provides a more precise and more accurate mean value (than the arithmetic mean) along with new dynamic endpoints for improved screening, diagnosis, prognosis and timely and timed treatment *(Fig. 2).* Trends are those with growth, development, maturation and aging and also those with risk elevation or disease and treatment. Risk elevation may change amplitude or timing, but not necessarily the mean. The implementation of engineering for concomitantly resolving the external and internal schedules depends on telecommunications and telehygiene as well as telemedicine (5) 1) for universal chronobiologic education (to assume self-responsibility and self-help in health care); 2) by the interpretation of data from physiologic monitoring (complemented as a *sine qua non* by chronobiologic data analysis and interpretation of the results) and 3) from the monitoring of pertinent environmental conditions. Thus, the number of cases of catastrophic diseases could be reduced and quality (since preventive) health care made available to all.

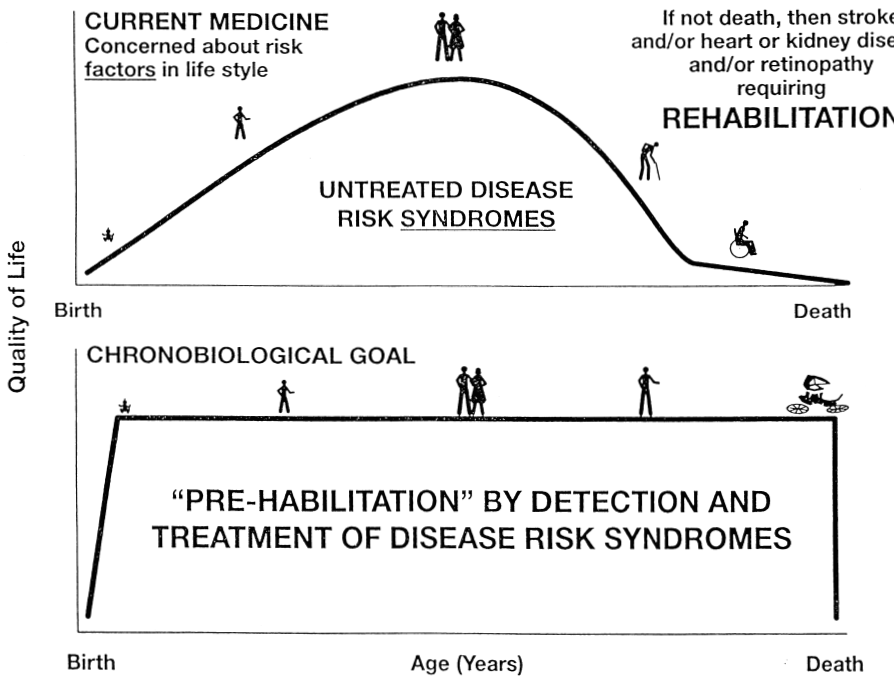
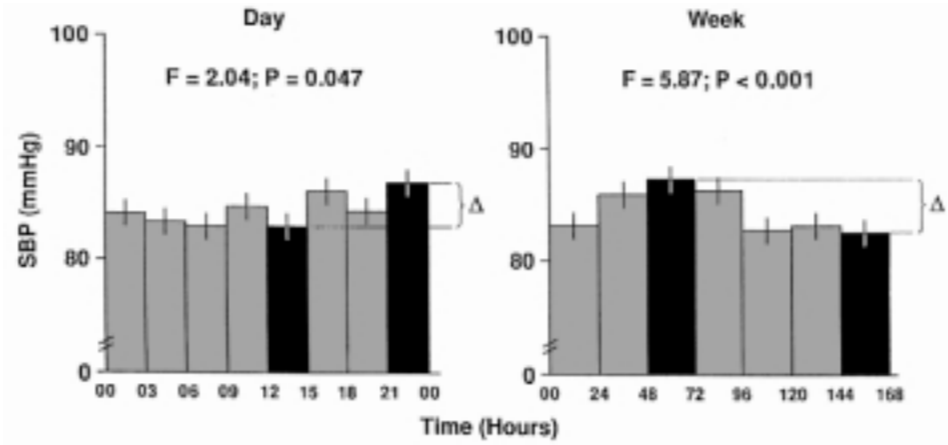


Fig. 2
Pre-habilitation preferably before as well as with rehabilitation (for vascular disease prevention and more generaly)

Toward such goals, the past half-century has provided the designs implemented first by self-measurements and desk computations and eventually the automatic methods, i.e., the hardware as well as software to debunk concepts of relative constancy assured by putative time-unqualified and hence viewed as time-independent feedbacks and feedforwards. Replacing such homeostasis is the recognition of a time structure, the chronomes. Originally, the race between East and West in space and eventually the now-ongoing international cooperation led to the development of biotelemetry (*6),* which is now routine in the laboratory and awaits inclusion in diagnostic and therapeutic devices. Such instrumentation for humans is available on the one hand with more and more sophisticated pacemakers, cardioverters and defibrillators as well as drug pumps on the therapeutic side. Among diagnostic devices, there are implanted heart rate monitors and more ambitious hemodynamic analyzers that record, with heart rate, also blood pressure, albeit as yet only on the right side of the circulation (*7*). The tasks on hand are, first, to improve the diagnostic devices to the point where they detect the earliest risk elevation rather than only overt disease; second, to render the therapeutic devices capable of preventive treatment (*Fig. 3)* and, third, to close the loop between the aforementioned devices to render preventive treatment automatic or at least self-implementable by the subject concerned (*Fig. 4*).



*** Around-the-clock SBP, detrended by fit of 5th degree polynormal, was used for folding (stacking) into an idealized day (left) or week (right); deviation of endogenous periods from exact day or week likely reduce extent of predictable change within each cycle**

Fig. 3
During first 4 months of very premature human life, circaseptan variation (Δ) in systolic blood pressure (SBP; right) is greater than the circadian (left)*

RESULTS

We are dealing with an old spinoff from the original excursions into space that yielded telemetry (*6)* and a potentially new one, stemming from endeavors in a budding chronoastrobiology. As humans venture deeper into space for longer time spans, it could be hazardous to ignore the demonstration of a new category of disease risk syndromes that, if recognized in time, may lead to the prevention of a massive stroke that could jeopardize a long-term mission in space *(2, 3).* Chronomedicine has shown that blood pressure overswinging (**c**ircadian

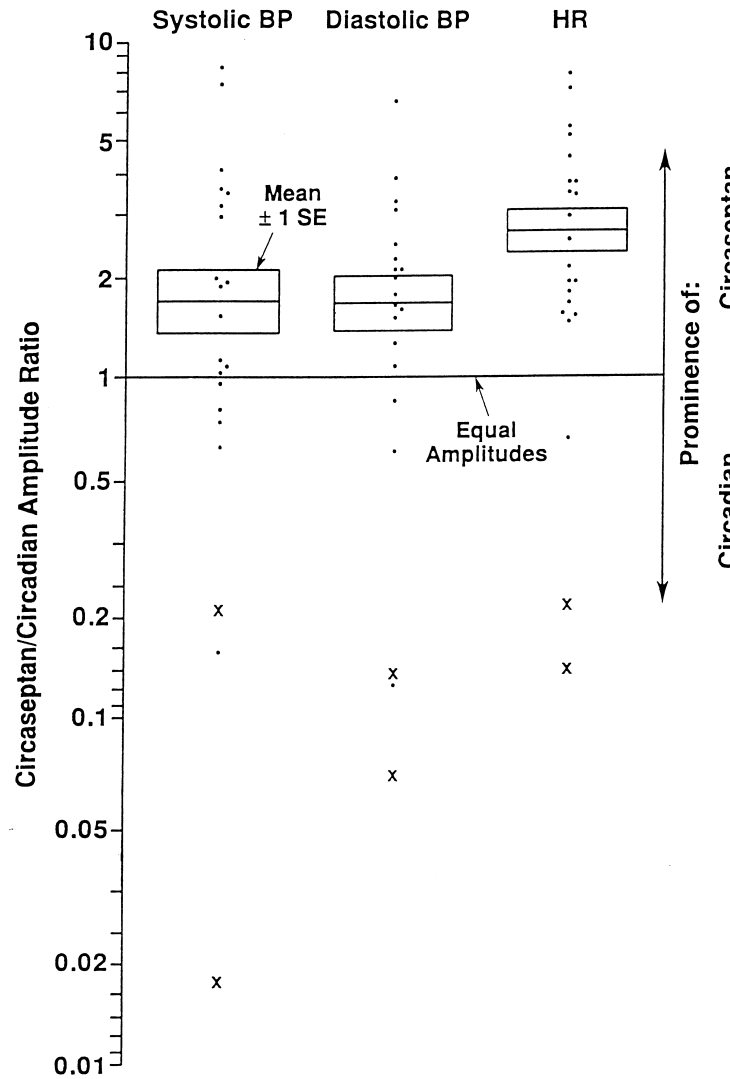


Fig. 4
Different circaseptan/circadian amplitude ratio of blood pressure (BP) and heart rate (HR) in premature neonates (•) and adults (x)

hyper**a**mplitude**t**ension, CHAT) is associated with a 720% increase in the risk of stroke, even in the absence of an elevated overall average pressure (*2*). CHAT is the largest risk factor among all those tested, and causes untold harm and expense. Human space travellers should be screened; otherwise CHAT may become the O-ring that leads to a biomedical Challenger disaster (*8).*

Chronoastrobiology

Chronobiology has shown a number of other „what-comes-firsts“ beyond the fact of interest to a preventive chronohygiene, that CHAT may precede the stroke. By the 1950s, a team of dozens of people could reproducibly show (what was incredible at the time, namely) that what was regarded as the most constant feature of our body, the nucleic acid, undergoes statistically significant changes along the scale of a day. What was even more surprising, for the then- and still-dominating dogma of a putative linear biochemistry (DNA RNA protein), was that in a single circadian cell division cycle, RNA synthesis precedes that of DNA (*9, 10*). One may argue, of course, that wherever one cuts a cycle is both its beginning and its end. But in the case of the growing mammalian liver, the marker „cell division“ displays an about-tenfold increase from near zero each day. There is also a sharp peak in DNA formation. In the context of DNA formation and mitosis, the growing mouse liver displays for a population what may occur in a single cell between two divisions. With the qualification that RNA formation also concerns nondividing cells, the mapping of nucleic acids raised the question of a temporal precedence of RNA vs. DNA, decades prior to the chemical evidence suggesting that an RNA molecule could have existed that naturally contained the sequence of information for its reproduction through reciprocal-base pairing and could also catalyze a synthesis of more like RNA strands: the RNA world, a stage in the development of life in which it is hypothesized that RNA molecules and cofactors sufficed to carry out all the chemical reactions necessary for the first cellular structures may well have occurred before our DNA world. If changes along the circadian scale mirror those along that of evolution, the precedence of RNA synthesis before DNA formation in the given cell cycle was the first hint of the chain of events in the course of evolution.

Next, we learned that a biological week is built into bacteria and unicellular organisms, another chronobiologic contribution, now to phylogeny (*11, 12*). As to ontogeny, the about-weekly change can be more extensive than the about-daily change, as shown in Brno (*13*) and elsewhere (*11),* and as it can also be in the early post-natal life of piglets *(14*) and rats (*15*).

The greater prominence in the postnatal stage of ontogeny of the week over the day suggests that perhaps life developed in the depths of the sea where the periodicities of geomagnetics with their about-weekly component were unencumbered by a competing about-daily periodic sunshine. The biological week also prompted computations to consider an ion world before the RNA world, if indeed the diffusion of ions in a weak magnetic field such as that of organisms exhibits a period close to a week (*16*). The week is perhaps the shortest harmonic with a stable long-term phase of the rhythmic Kp component of about 27 or 28-29 days, depending on the stage of the ~10.5-year Schwabe sunspot

cycle (*17*) to which life could latch on when it faced tasks such as those in immunology and repair, which could not be accomplished in a day, but could be accomplished within a week, a hint of an internal evolution (*18*).

DISCUSSION

Whether astrobiology is interested in the origins of life or in the health of humans venturing into space, the question what comes first can be extended to the general inquiry into the mechanisms of changes within the normal range. Thus, as an indispensable first step, there is a need for mapping these changes. This is the purpose of the BIOCOS project which collects reference values systematically for blood pressure and heart rate, and opportunistically for other variables to align time series from the Biosphere with those in the Cosmos, and thus to detect influences of events in the latter upon our health and agriculture, and perhaps also on political events on earth (*19*).

The challenge to manufacturers as well as to their engineers is thus to do more than the equivalent of the black box of an airplane. The latter informs us about what happens after the *fait accompli* of a crash, as did the autopsy in classical pathology. We can use the currently available software for repeated passes over a time series, as it accumulates. For instance, a beat-to-beat electrocardiogram is already available, from an individual monitored for a year in apparent health. Blood pressure has been recorded mostly at 15-min intervals for over a decade. We can then summarize variability along the frequency of the cardiac and then of the respiratory cycle and can use cardiac and then respiratory rhythm characteristics as compacted endpoints for summaries via further repeated passes for the analysis of longer and longer data sections to assess rhythms with lower and lower frequencies. These broader and broader spectral windows on more and more data, with more and more compacting, can fit into an affordable memory for storage, so that the analyses can continue as a feature of recycling. Each new analysis then provides endpoints for the analyses of rhythms with even lower frequencies. It thus becomes pertinent, although it sounds utopian, to exploit the most recent information on 10- or 20-year cycles that are apparent in biological data as well in the sunspots, where they were found by Schwabe in 1843. The spinoff on earth, from such data of interest to those who travel into space and thus to a chronoastrobiology, is the development, for the next fair, of the appropriate instrumentation that can detect blood pressure overswinging. **C**ircadian **h**yper**a**mplitude**t**ension, briefly CHAT, as noted carries the greatest risk of stroke. It is to be avoided as best one can, not only during space travel, but for all the many persons at risk on earth. This task is as important for vascular disease prevention and treatment (*25*), and is as much in the public domain, as are vaccinations for infections.

At each fair, those with the privilege of opening it have the task of trying to learn from the past in order to indicate what can be offered for the future. Our

suggestion to engineers and manufacturers is a new family of devices that are diagnostic in that they recognize rhythm alteration early and eventually become therapeutic as well, by acting to lower the risk found to be elevated. The earliest chronome alteration may occur in a number of cases on rhythms of relatively low frequencies, e.g., as a circannual rather than circadian rhythm alteration in the case of an elevation of breast cancer risk *(20, 21*). The successive automatic windowing, compacting and recycling then becomes essential. It allows the data to be interpreted as-one-goes, a requisite for tests of preventive countermeasures, in response to the earliest warning.

The attentive visitor to this fair may look for the combination of hardware tools that, when joined to the software for windowing, compacting and recycling through repeated passes, can usher in a system wherein the instrumentation replaces much health care personnel. In order to achieve this aim, literacy becomes essential in the chronobiological specialties of a chronotelehygiene of prevention to be implemented by every person as a complement to the chronomedicine concerned with overt disease. The reference values collected in this practical endeavor of physiological monitoring may also serve a basic and applied chronoastrobiology in the context of cross-spectral analyses with the incoming stream of information gained from space-borne vehicles. When, in one case thus far (*22*), the blood pressure studied by superimposed epochs rises before a southward turn of Bz, the vertical component of the interplanetary magnetic field, it is worthwhile to scrutinize such time relations on added cases. Both our pressure and Bz may respond to as-yet unidentified events, within or even beyond the solar system and the behavior of the pressure on earth may prompt a scrutiny of remote events. Visible light is indeed an important environmental switch (*23, 24*), but not the only one. Sunspot cycles and their signatures in geomagnetic disturbance play an added role (*26*). Neither is master or slave: they are elements in a collateral hierarchy of interacting chronomes in variables within and around us. By monitoring humans eventually from womb-to-tomb, the chronobiologist may study the ontogeny of one species. By the added monitoring of several non-human species, we align ontogeny with phylogeny to explore cosmogeny (*22*). Thus, we may learn where we come from, to better attempt to choose among the directions into which we can evolve.

Halberg F.,. Cornélissen G, Watanabe Y., Siegelová J., Fišer B.

OD ČASOVĚ NESPECIFIKOVANÝCH MĚŘENÍ K CHRONOBIOLOGICKÝM PŘÍSTUPŮM JAKO JE CHRONOMEDICINA A CHRONOASTROBIOLOGIE: VÝZVA VÝROBCŮM

S o u h r n

V minulých padesáti letech byl nastíněn problém chronobiologie. Zpočátku se používaly metody samoměření fyziologických veličin a výpočtů, a nyní je k dispozici monitorování a výpočty pomocí počítačů. Biotelemetrie pro měření funkcí člověka je nyní velmi dokonalá, doplňuje použití

pacemakerů, přístrojů pro kardiovezi a defibrilátorů, stejně jako používání dávkovacích pump na infuzní léčbu. Diagnostické přístroje zahrnují implantované monitory srdeční frekvence a dokonalé hemodynamické monitory, které zaznamenávají kromě srdeční frekvence i krevní tlak, i když zatím pouze na pravé polovině srdce. Dalším cílem je zlepšování diagnostických přístrojů tak, aby zjišťovaly včasné riziko spíše než rozvinuté onemocnění, terapeutických přístrojů schopných léčby a spojení obou principů, tak aby preventivní opatření byla automatická a léčebná opatření byla k dispozici i samotným nemocným.

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