1996

"FROM HOMEOSTASIS TO CHRONOME"

The transition from a single sample medicine (that needed the rationalization of homeostasis) to each variable's time structure (chronome) is slow to come about. If it does enter the mainstream of health care, this eventual achievement will represent the fruits of work and fun by all of those listed in the following bibliography and many more. It is the more promising that the motto of this greeting quoted above is the title chosen by Life Science Publishing of Tokyo for a publication in Japanese summarizing a recent interview with us. It is available on request from us in English by e-mail only.

The chronome story began with the long-known biological day, exhibited by plants whose "sleep" movements were described by Androsthenes in the fourth century B.C. The path over the biological week now leads to the half-week, which can represent not only a non- sinusoidal week, but also a component in its own right.

For the week, we turn back to Hippocrates. That the week is built into us was known to him and to others in antiquity. There was an about 7-day interval between the appearance of symptoms and turning points such as death or cure, i.e., crisis or lysis, known even to one of us, who saw patients before sulfonamides and antibiotics truly miraculously changed the outcome of many infectious diseases. Evidence for a 7-day periodicity comes from the fact that the pattern repeats itself in the ensuing 3-4 weeks, albeit with a somewhat dampened amplitude. In our lifetime the biological week (circaseptan) was repeatedly rediscovered. Often, it was as a feature of pathology or at least as a response to unusual stimuli, in health or disease. Some of these stimuli were as drastic as an organ transplant or the removal of a kidney; another stimulus was a massive dose of testosterone that may have led to a free-run of the week assessed longitudinally over a 3-year span. Still other stimuli were as mild as a visit to a spa; the week appeared to be a response to them (1). The time-macroscopic effects of a stay in a recreational setting, i.e., obvious weekly patterns, were described by Gunther Hildebrandt with Ingrid Bandt-Reges, in a highly recommended scholarly review of circaseptans (1; cf. 2, 3). It must be remembered in this context that a single stimulus carries no 7-day information.

The "reason" for circaseptans as an adaptation to the environment was not clear to us. In the want of known regular about-7-day environmental cycles, the biological week appeared to be integrative, as a feature of a then-postulated internal evolution. One of us interpreted a 6.9-day period as free-running when he first had a chance to see this periodicity prevail for the last several years of a series covering 15 years of 24-hour collections of urine for the determination of 17-ketosteroid excretion (as well as urine volume, which remained 7-day synchronized) by a friend, the late Christian Hamburger (4).

While leading geophysicists kindly dissuaded us from "wasting time" on spectral analyses of geomagnetic disturbance, the past few years brought not only the demonstration by us (5) of a circaseptan in the planetary geomagnetic disturbance index, Kp, which constitutes the summary of reports from a total of 13 different stations around the earth, on both the Northern (11) and the Southern (2) hemispheres. In our analyses (published in 1991) of the data from 1932-1990, overall we found a 6.74-day periodicity for Kp. Juan Roederer (6) deserves the credit for the confirmation and extension of our finding by showing different (unpublished) spectra during the ascending and descending stages of the solar cycle, "isolating" a 6.9-day periodicity in Kp during the descending stage. Hamburger's free-running period in 17-ketosteroids was close to 6.9 days. It then took us a chronobiologic serial section to find that at least there was no consistent phase relation between the wobbly circaseptans of Kp and the concomitantly studied more stable circaseptans in 17-ketosteroid excretion (5).

We have not (yet) examined whether 17-ketosteroids and Kp during the span of the former's free-running showed overall the same frequency. In a recent 267-day isolation study in Italy, however, a nearly half-weekly (circasemiseptan) periodicity in heart rate stood out clearly (7). It was "free-running" from the social half-week, but in this case there was a very close (nearly identical) period of 81.5 hours in Kp.

Speculation. Could it be that we still resonate with planetary magnetic disturbance by sharing its frequency even if we do not phase-lock into it, and over short spans are not synchronized in phase with Kp? We saw that phenomenon of frequency synchronization without phase-lock in circaseptan studies carried out first with Dora K. Hayes at Beltsville with face flies (8). The circaseptan phase was very irregular. There was, however, a 7-day pattern of responses to shifts of the environmental lighting regimen at different intervals.

Could it also be that for most if not for each of our physiological rhythms (2), there is and/or was an environmental cycle with a near- match in frequency, to which one or the other function in one or the other organism locked-in (9)? Environmental cycles that are shared by many forms of life may be those that have been around for the longest span? We do not know the answer, but it seems to be worthwhile to seek it, while keeping in mind the other side of the coin, namely that functional coordination requires integration within the organism as well as adaptation to cycles in the environment, another broader aspect of integration or coordination. Some of the body's rhythms may be primarily integrative, even if they reveal adaptive features. One does not exclude the other. Adaptation is merely integration at a broader-than-organismic level.

Our further demonstration during the past year of not only added 7- but also of added 3.5-day components, not only in Kp, but also in other biological time series, is pertinent for the postulation (mainly by Hildebrandt; cf. 1) of such an adaptive aspect to the biological week.

Newly developed methodology on the one hand made allowance for a wobbly period by using as the characteristic frequency that associated with the highest amplitude in a given frequency region (e.g., in the about 1 cycle/week region) during a given data span analyzed (e.g., of a year). On the other hand, a complementary analysis examined the power or the normalized power contained in a broad band (e.g., around 1 cycle/week). Thus, we looked for both frequency and amplitude modulations of the week and half-week by the about-11-yearly cycle of solar activity.

Whereas the about-weekly component shows a modulation by the solar cycle somewhat similar to that of the about-monthly and half-monthly Kp components related to the solar rotation, the about 11-year modulation of the half-weekly component differs while also differing from the behavior of noise, suggesting that the signal-to-noise ratio may be too low around 84 hours to reliably estimate the solar cycle modulation of a circasemiseptan feature of Kp, documented to be statistically significant by population-mean cosinor during the descending phase of the solar cycle. The results on circaseptans and circasemiseptans in Kp were shown in a number of abstracts published this past summer (10-13).

The reasons for the search at first are purely physical; next, biologically they exceed by far the look at the health effects of magnetic storms, even if an increase in myocardial infarctions (MIs) in Moscow after an interplanetary event (a southward turn of the vertical component of the magnetic induction vector, Bz) was documented in 1991 in inferential statistical terms (5). It was confirmed for MIs and extended to strokes by a different approach (14) and in the case of MIs confirmed for a different, albeit nearby, geographical area by Villoresi et al. (15), as reviewed in part, and in a broader context, by Roederer (6). The data accumulate that should prompt a test of any merits to including stormy weather in space in the earthly routine weather report, notably since a decrease in heart rate variability (which has been associated with the risk of coronary artery disease) has been documented even in very fit individuals (cosmonauts) during a magnetic storm (16).

A remove-and-replace approach was applied to examine physiological effects that may at least complement and perhaps underlie, as triggers, the pathology related to magnetic storms. An about-weekly resonance was found at this scientific frontier (12). Sooner or later, a coordinated denser physiologic and physical monitoring by ambulatory devices will be indicated and discussed, perhaps in the context of the next meeting in St. Petersburg, June 30-July 7, 1997, of the International Union of Physiological Sciences, which will feature a symposium on "Adaptation to the Environment". Please contact us if an invitation can help you secure local or national funds for your participation in the planning of international monitoring.

An implanted beat-to-beat monitor has been built and implanted and is being tested on ambulatory patients with heart failure. In a 15- month record, a chronome (time structure) analysis carried out blindly (17) revealed rhythm alterations that could be related to changes in the patient's treatment, as was a sharp decrease in overall heart rate variability gauged by the standard deviation, the current focus of interest. Without implying causal relations (post hoc ergo propter hoc reasoning), as a minimum the complementarity of the chronobiologic methods that had two alterations in the normal range can be documented.

The immediate clinical frontier this year, as in the last few years, revolves around the behavior of the amplitudes in the spectra of blood pressure and heart rate. In transverse measurement series that cover at least 7 days, the chronome of blood pressure has been studied for the entire human lifespan (18). Denis Gubin of Tyumen, Siberia, found early and late in human life that circaseptans and circasemiseptans are much more prominent than in adults. Whether the focus is on aging or on stroke prevention, those dealing primarily or exclusively with the period and phase of circadians, as a feature of biological time measurement, lose out in extremely important clinical

and basic dimensions. The 7-day profiles also served to document the limitations of a 24-hour record (19).

In order to bring chronobiology into the mainstream of health care, it is important that the excessive circadian blood pressure amplitude named by us "Circadian HyperAmplitudeTension" (briefly, CHAT) be tested in a true chronotherapy, but only after a rigorous chronodiagnosis (20, 21). CHAT is a newly discovered clinical entity (22-24). For part of the day, pressures are too high; for another part, too low. Serial measurements around the clock are thus mandatory to get a reliable diagnosis, as is the replacement of current fixed limits by time-specified limits (chronodesms) (25). Treatment at the wrong time (lowering blood pressure when it is already too low) could do more harm than good. The treatment of CHAT will have to be optimized in terms of the best time, not only for drug but also for non-drug treatments such as autogenic training (26-28). This task could be of great importance to health care since strokes not only cost $30 billion a year in the U.S. alone, but they are the greatest crippler and cause of suffering.

Highlights this year were the finding of a circasemiseptan component for the most potent vasoconstrictor, endothelin-1, in Brunetto Tarquini's data from Florence, with an altered pattern in the presence of vascular disease risk. This newest circasemiseptan follows their demonstration in the elderly (18) as well as in early human extrauterine life, as documented in Minneapolis, Florence (Italy), La Coruna (Spain), Brno (Czech Republic), Moscow (Russia), Yamanashi (Japan), and elsewhere, as well as their demonstration in pro- and eukaryotic unicells (2).

Not yet written up are circaseptans in the temperature of pigs by Dinand Ekkel of the Institute for Animal Science and Health in Lelystad, The Netherlands, and circaseptans and circasemiseptans in hourly sampled data on pancreatic variables of piglets on the days following weaning by Mary-Jane Thaela at the University of Lund, Sweden. As to mechanisms, hints are provided by the finding of circasemiseptans after the enucleation of Acetabularia in the response of its growth pattern to shifts in the lighting regimen (29), which in the intact giant alga exhibits a circaseptan pattern. Circasemiseptans also characterize the beating of a myocardial cell (30) or a retina's firing in vitro (31).

The last manuscript (by FH) prepared and now completed for submittal for publication discusses the Cornelissen-series. This is a series of the ratios of measures that describe the relative prominence of the biological week and half-week (the circaseptan and circasemiseptan components of our time structure) compared with the circadian. These are just a few components of what in the 90s we have called the chronome (32-34). A chronome characterizes every biological data series, if it varies nonrandomly and exceptions to non-random variations as yet are not found. We coined the term originally to indicate not only that there is a rule (=3D nomos) for changes with time (=3D chronos) but also that in living things changes, at least in part, are genetically anchored. To make this point, we used the ending "-ome" from "chromosome".

Eventually, we encountered, after much searching, counterparts in inorganic nature for some of the components other than the obvious day and year: very subtle ones, as Frank Brown Jr. would have put it, even for a 3.5-day component, as outlined above, with added substantial evidence in the thesis by Dewayne Hillman based on cross-spectral coherence (35). Christopher Bingham and Hans Wendt looked out so that their chronome endeavor did not stray too far from a rigorous

analytical statistical or geo- and astrophysical path, respectively. It became obvious that we should speak of rhythm and chronome in analyzing the time structure of any variable, biological or other. We are doing what the physician William Gilbert did when writing his De Magnete (36) and the geophysicist Juan Roederer emphasizes (37): the tearing down of interdisciplinary barriers. The ratios of what FH has named the Cornelissen-series, however, as yet are only biological. They are formed by the 7- or 3.5-day amplitudes, each expressed in relation to the reference standard of the circadian amplitude. This choice of ratios was made originally after at least the 7- or the 3.5-day rhythm was found to be statistically significant, but statistical significance does not enter into the computations of these ratios, obtained by fitting cosine curves with 7-, 3.5- and 1-day periods to the data.

We re-emphasize that the chronome is a concept much broader than that of multifrequency rhythms and their interrelations such as those of the multiseptan (integer multiples or submultiples of circaseptan) components of the Cornelissen-series. Any variable, inorganic or organic, is likely to undergo, with its periodic variations, also trends in the characteristics of each of these multifrequency rhythms and further trends in the characteristics of deterministic and other chaos. Chronomes are found, e.g., in meteorological variables, and the word "chronome" then implies that rhythmic and/or chaotic endpoints of these variables reveal some rule (nomos) in time (chronos). In a biological context, as noted in the foregoing, the ending "-ome", as a portmanteau formation similar to the coinage of "genome" conveys the circumstance that the biological cycles and the trends they undergo are in part anchored in the genes. This is why we coined "chronome" in the first place. We now find that some components of the chronome can have at least numerical counterparts in nature, suggesting a phenomenon of resonance, even in the relatively high-frequency regions of the EEG and ECG, which may show associations with Pc-pulsations. We could document resonance by a remove-and-replace approach for the circaseptan amplitude of heart rate, in association with circaseptans in the velocity changes of the solar wind (2, 12). At this point it seemed logical to extend the chronome concept to inanimate nature.

On the practical side, we re-emphasize the importance of testing for both physiological and pathological effects of stormy weather in space. We conclude by adding to the clinical emphasis on CHAT (blood pressure overswinging) the documentation that this condition needs a chronodiagnosis and that once validated it can be treated (22-28).

On the basis of this and other evidence presented to him, Donald Marquardt, who was at the helm of statistics of both Du Pont and the American Statistical Association, and still does an international job for the U.S. government, suggested that the time to bring chronobiology into the mainstream of health care is now. We may have applied opportunities to do it, but for the moment we are all having fun in basic science, until the tools and systems become available to bridge the gap into everyday self-help by the chronobiologically literate person. Bringing such literacy about is a task for all of us in the chronome endeavor and beyond.

There remains work to do and these are the best thoughts for holidays and for New Year resolutions. While we thank so many for steadfast cooperation in the past, a more complete report on where cooperation in a modest yet productive international chronome endeavor is leading us at this moment consists of the titles of publications that represent this year's endeavors (and of course build on many of the previous decades' learning and fun). A recent bibliography, along with

a list of meetings to which the chronome endeavor contributed, follows at the end of this report. More is available on our home page (http://revilla.mac.cie.uva.es/chrono). Chronobiology is indeed complex. Chronomes, like chemicals, must be isolated. The only alternative is biology and medicine in a stage equivalent to alchemy.

Chronobiology is like a beautiful puzzle with the different pieces constituted by the different components of the chronome on both physical and physiological variables, slowly coming together and providing new glimpses of the "whole picture". As important as it may be to find and place the last piece, there is no need to postpone any longer the implementation of a true chronomedicine since any single piece of the puzzle is sufficiently informative of the very large limitations of homeostatic thinking and constitutes the bridge from after-the-fact cure to prevention. Chronobiology offers not only many findings daily, but there is also much debt in each new fact.

With thanks for reading thus far and even more gratitude should you act on the foregoing, and with best wishes,

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