

# Essays on Chronomics Spawned by Transdisciplinary Chronobiology

## Witness in time: Earl Elmer BAKKEN

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### Foreword

Technology allows the monitoring of ever denser and longer serial biological and physical environmental data. This in turn allows the recognition of time structures, chronomes, including, with an ever broader spectrum of rhythms, also deterministic and other chaos and trends. Chronomics<sup>1</sup> thus resolves the otherwise impenetrable “normal range” of physiological variation and leads to new, dynamic maps of normalcy and health in all fields of human endeavor, including, with health care, physics, chemistry, biology, and even sociology and economics. The authors plan to describe initiators of modern mapping of our make-up in time, with focus on mechanisms and applications. Earl Elmer Bakken, to start the planned series, is also to serve as a local time-witness (*Zeit-Zeuge*) of concerns about chronomics in Minnesota.

### Introduction

Genetics, as a quantitative science, took a long time to develop into genomics and proteomics. Gregor Mendel, and even those who rediscovered rules to inheritance long buried in Mendel's original findings were all dead by the time the mapping of the human and other genomes was initiated. By comparison, the development of chronobiology as an inferential statistical science resolving variability in time was fast. Rather than being viewed by a few others, [1-7; cf. 8], here preference is given to assays that may be checked by those described themselves.

Karl-Heinz Bernhardt (9) quotes Goethe: “... die Geschichte der Wissenschaft die Wissenschaft selbst, die Geschichte des Individuums das Individuum ist” (“The history of science, the science itself, is the story of the individual, is the individual”). This view applies not only to those sharing Goethe's view of nature, which again according to Bernhardt emphasized what is obvious to the naked eye, such as the classification of clouds by Luke Howard, to whom Goethe dedicated a poem (9). Precisely as in dealing with the form of clouds, as a pertinent example, Goethe focused on what can be seen with the naked eye — that is he sought primarily what he presumed not to have been able to find in numbers and signs (“Goethe, in seiner Naturbetrachtung immer vorrangig auf das *dem Sinne der Augen Erfassliche* fixiert, griff die Howardsche Wolkenklassifikation enthusiastisch auf, eröffnete sie ihm doch einen seiner *Neigung und Lebensweise angemessenen* Zugang zur Witterungskunde, den

er über Zahlen und Zeichen nicht hatte finden können, wie er in der *Wolkengestalt nach Howard* ausführte.”) This time-macroscopic approach can be a starting point for chronomics but is not our concern herein.

We take a view that neither may be improperly labeled as diametrically opposite, nor does it deprecate either Goethe’s incontestable genius or the stature of many opinion leaders in the field of clocks. We echo Alexander von Humboldt, who courted Gauss (10) by presuming first that everything in science is to be expressed by at least semiquantitative numbers and signs. We add that these numbers (the point estimates) are at best accompanied by estimates of their uncertainties, such as 95% confidence intervals. This is neither to say that intuition and/or a keen observation without numerical support is inappropriate: it is often the best start of an investigation. We will also elaborate on the merit of responding to a problem promptly, with the first available tool, as by the use of a metronome in an initial application to cardiac pacing (11). Eventually, improvements are to be guided by the results of numerical analyses (12–15), but again one must not rely on inferential statistical analyses alone. Furthermore, whenever the transformation of an observational series from the time into the frequency or phase domain is required, the back-transformation into time is desirable (16–20).

Science cannot proceed without figurative microscopes in time as well as in space. The analogy to the need for detecting, for instance, the lurking dangers of infection by unseen microbes before they lead to hard events, including death, applies necessarily to the merits of mapping structures in time, chronomes, to detect disease risk syndromes in blood pressure and heart rate variabilities (19). Cartography in both space and time with the use of tools that extend our senses to resolve “unseen” matter is very often indispensable (6) and is of transdisciplinary theoretical and applied interest (18–20; cf. 5, 16, 17).

Whenever possible, we return to Goethe’s position, described figuratively as a spiral, by trying to revisit, visualize and check at a higher, invariably numerical level along the desirable and often indispensable scale of time, whatever was found in the frequency and phase domains. This is the scope of chronobiology, as it developed from intuitive observations of within-day and seasonal variations to the mapping of the time structures, chronomes, in us and around us, that represent the dynamics of everyday physiology, psychology, pathology and even of everyday economics. All human endeavors can benefit from the cartography of transdisciplinary chronomics, Figure 1. The many who contributed to chronobiology and thereafter to the necessary systematic mapping of chronomics in our era and earlier cannot all be singled out again (16, 17); the authors are deeply in their debt.

*Ubiquity and relative prominence of biological near-matches of photic and non-photoc environmental cycles.* The first anthropoids shared with other animals and plants the recurrent, nearly daily periodic need for rest or sleep (21–24) or at least the need for a recurrent change from anabolism to metabolism. Thus, rhythms, if not chronobiology, became obvious before *Homo sapiens* developed. Circadians characterize most early living matter, bacteria included (25). The endogenous preparation for rest each night, or for each awakening, is a basic feature of our physiology as in the sleep movement of plants (26–29) or in the motor and other rest-activity cycles. Almost every body function of plants and animals may carry genetically coded photic interactions with the earthly daily alternating light-dark environment (30). But non-photoc effects are also likely.

Why is the biological week more prominent than the circadian rhythm, e.g., in the electrical activity of a single cell that may have been around on earth 500 million years ago (31)? Again, why is the biological week more prominent than the day early in crayfish, rat, piglet and human ontogeny (32, 33)? Why does RNA formation precede DNA synthesis in each

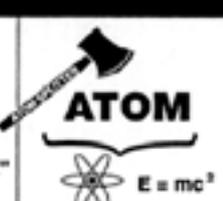
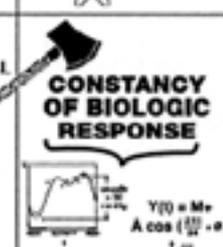
CAN CHRONOBIOLOGY CHANGE FUNDAMENTALLY THE WAY HEALTH CARE IS PRACTICED?*			
FALSE BELIEF	EVENT	NEW SCIENCE	BENEFIT
<p>THE SMALLEST PARTICLE OF MATTER IS THE “UNSPLITTABLE” ATOM</p>	 <p><b>ATOM</b> <math>E = mc^2</math></p>	<p>NUCLEAR PHYSICS YIELDING FROM MASS</p> <p><b>ENERGY</b></p>	<ul style="list-style-type: none"> <li>- electrical power</li> <li>- military use</li> <li>- industrial use</li> <li>- propulsion</li> <li>- space applications</li> <li>- medical use</li> <li>- understanding the universe**</li> </ul>
<p>THE RANGE OF NORMAL VALUES (below a FIXED LIMIT of 140/90 mmHg for blood pressure) is “UNSPLITTABLE”</p>	 <p><b>CONSTANCY OF BIOLOGIC RESPONSE</b> <math>Y(t) = M + A \cos\left(\frac{t - \phi}{\tau}\right)</math></p>	<p>CHRONOBIOLOGY YIELDING INFORMATION FROM RHYTHMS, TRENDS, ...</p>	<p>Improved health care at much less cost</p> <ul style="list-style-type: none"> <li>- timely and timed treatment of disease</li> <li>- disease risk lowering and prevention</li> <li>- more economical laboratory and other measurements</li> <li>- better understanding of body and mind functions leading to high tech and high touch health care</li> <li>- understanding the universe**</li> </ul>

Fig. 1. Today, the normal range is the time-unqualified reference standard in all science. We find it with every laboratory determination in biomedicine. In many other fields, normalcy is assessed as a deviation from this range. It was once believed that the “atom” was the smallest particle that could not be further split. Breaking the atom opened the door to a new universe of particles governed by new forces and physical laws. The field of nuclear physics evolved and brought with new knowledge a new energy source and a wealth of practical applications. Similarly, lifting the curtain of ignorance hiding the range of physiological variation uncovered a new world of biological functions that, instead of striving for constancy in a homeostatic framework, consist of time structures, chronomes. These consist of deterministic and other chaos and trends coordinated by rhythms, the backbone of life itself. Entering the physiological range revealed new biological laws and yielded new information, the task of chronobiology and the mapping of chronomes or dynamic gene expression, chronomics. © Halberg.

1. Chronomics is a quantitative, inferential discipline with methods for serial (preferably automatic) data collection and (preferably automatic “on line” as-one-goes) data analysis. This discipline provides a temporal cartography; it maps make-ups in time, or chronomes, in and around us. Intermodulations among chronomes, the feedsideways, by far exceed the scope of biological calendars and clocks on the one hand and of time-unqualified feedbacks and feedforwards on the other hand. By resolving feed-

sideways—chronomics—curtains of ignorance drawn by the concept of an acceptable but negligible normal range of variability over everyday physiology are replaced. Maps in time are provided instead, for interpreting a time-specified single sample and preferably for evaluating a time series. Chronomes replace an imaginary baseline based on the assumption that there is relative constancy and reveal the dynamics occurring between the upper and lower limits of putative and, since time-unspecified, spurious

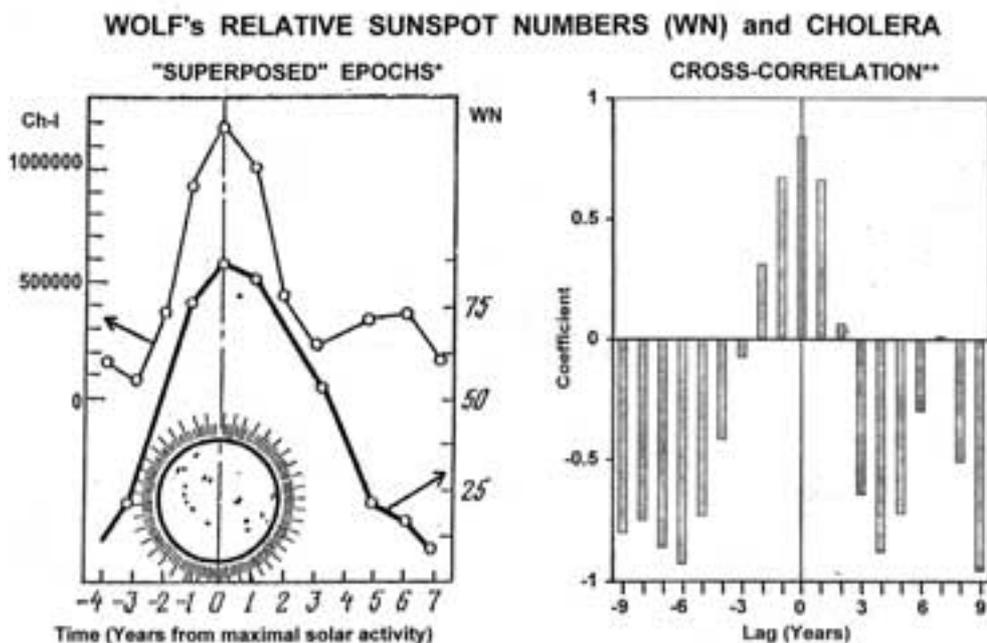
acceptability. For instance, with maps of circadian parametric and non-parametric blood pressure characteristics, we no longer try to find the true blood pressure or true heart rate. Instead, we focus on indispensable information from the rules of variability that are important personally to both Earl and the authors. Herein, we document and illustrate the need for a chronobiologic data interpretation, even when we deal exclusively with values that are neither too high nor too low, but vary abnormally.



**Fig. 2.** Alexander Leonidovich Chizhevsky (1897-1964), regarded as the father of heliobiology, who time-macroscopically described life on earth as “an echo of the sun” based on an approach with superposed epochs to the ~10.5-year Schwabe cycle of solar activity. Adapted from Sigel (50).



**Fig. 4.** Frank Brown Jr. (Feldafing, Germany), photographed by Prof. Franklin Barnwell, his then-fellow and associate in research. We owe to the school of Brown and Barnwell the US concerns about subtle factors and the paraphrasing of free-running as “autophasing”.

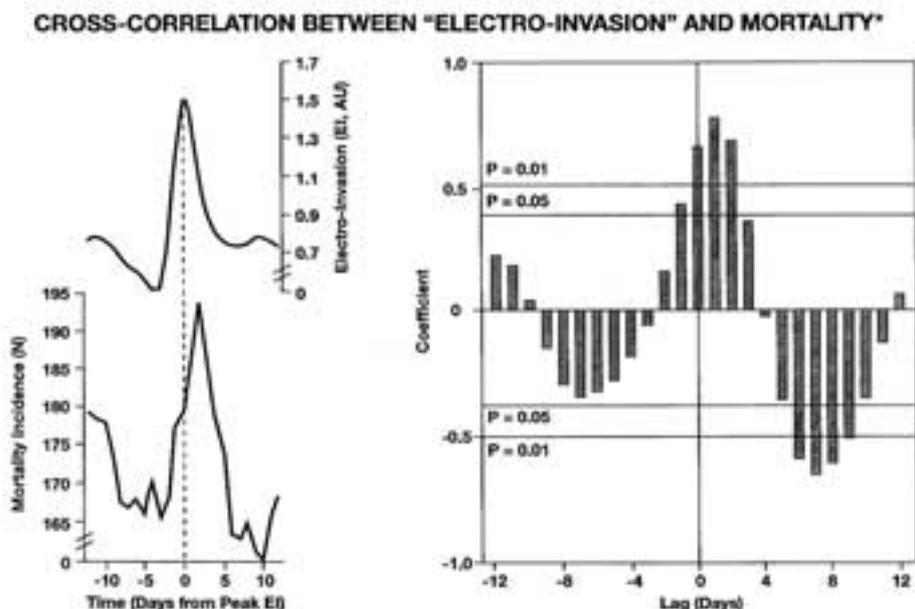


**Fig. 3.** Data from A.L. Chizhevsky on cases of cholera recorded in Moscow between 1823 and 1923, originally folded over an about 11-year solar activity cycle, showing a peak incidence coinciding with maximal solar activity (left). Data taken off the published graph, analyzed by cross-correlation, corroborate that the largest correlation corresponds to lag of zero (right). Should the original 100-year series have been available for analysis, a measure of uncertainty could have complemented the average curves (left). © Halberg.

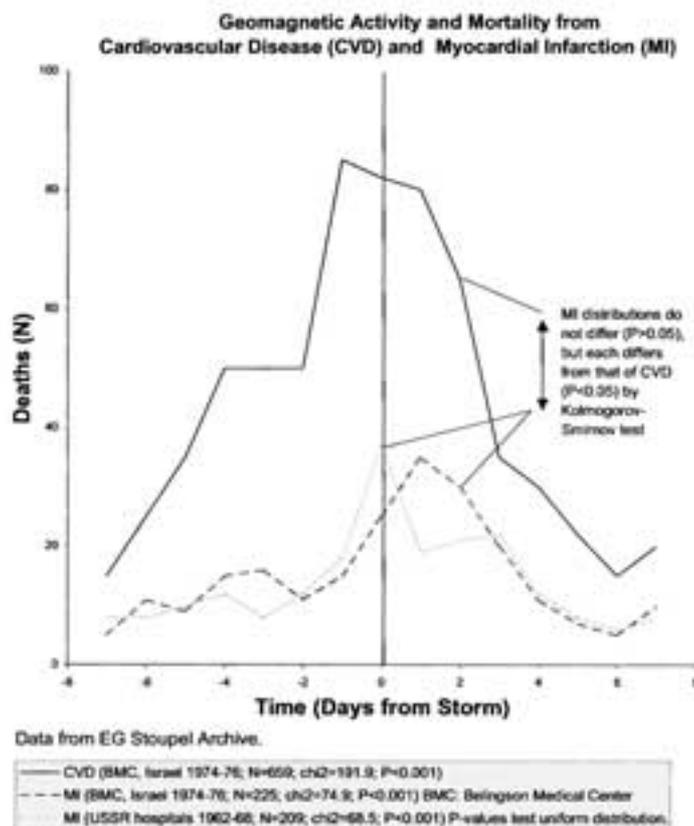
murine circadian hepatic cycle (34, 35)? A budding chronoastrobiology may scrutinize the possibility that such findings constitute a separate line of evidence supporting an RNA-world before a DNA-world. Moreover, the prominence of the week early in ontogeny and phylogeny, is in keeping with the resonant frequency of ions in a weak magnetic field, involving periodicities of about a week (36). Is it also in keeping with an even earlier prebiological, if not primordial biological electrolyte world (32)? In this context, early stages of ontogeny may constitute living fossils (37).

*Subtle cosmic/magnetic factors?* Human pathology (38), suicides (38, 39), epilepsy (37), heart attacks (37, 40-47; cf. 33), strokes (44, 45, 48) and traffic accidents (49) have been investigated for associations with geo- or heliomagnetics, controversies (41, 42) arising perhaps because of a solar cycle number- and stage-dependence of susceptibility (33). Human morphology, psychology and behavior, normal as well as abnormal, by virtue of cyclic signatures, cross-spectral coherence and remove-and-replace approaches (37) also show associations with non-photic effects of the sun and/or galactic cosmic rays. Planetary magnetics constitute not only an endogenous feature of the earth itself, but also a partial signature of effects from the sun and from beyond it.

Subtle factors are a matter of the unequalled lifetime concern of A.L. Chizhevsky (50-53), Figure 2, whose expressiveness was matched by extensive albeit descriptive statistical data, those in Figure 3 fully confirmed by meta-analyses. Traute and Bernhard Düll (38), and Frank A. Brown Jr., Figure 4 (54-57) and Franklin Barnwell (58) have considered the roles played by subtle factors. Whereas Chizhevsky superposed 11-year cycles in the incidence of cholera, Figure 3, the Dülls used 27-day cycles of other pathology, Figure 5. Their propositions are supported again by time-microscopic tests, as is the work by Stoupele, Figure 6 (40). The time-macroscopic study of chronomes — structures in time — in both geomagnetism and chronobiology, however, has a long, albeit descriptive history (59), with some notable exceptions (60-63).



**Fig. 5.** In data of Düll and Düll, who summarized the incidence of brain-related human mortality in relation to “electro-invasion” by superposed epochs over 67 solar rotation cycles (left), we find a maximal cross-correlation at a 1-day lag (right). By “electro-invasion”, the authors referred to “short-lived” eruptions on the surface of the sun (M-regions of the sun, presumably corresponding to what is now known as coronal mass ejections); the electrical particles ejected by these solar phenomena, when they reach the earth, elicit “electron invasions”, the extent of which is characterized by the extent of disturbance of the electromagnetic field. © Halberg.



**Fig. 6.** Meta-analysis of data from E.G. StoupeI presented and properly analyzed by him as superposed epochs of deaths from cardiovascular disease (CVD) in Israel or myocardial infarctions (MI) in Israel and the former USSR. The peak mortality observed near the day of a magnetic storm is statistically validated by a chi-square test for uniform distribution. The difference in mortality between quiet and stormy days had been found and rightly championed earlier by Prof. StoupeI himself. Differences in the patterns of CVD vs. only MI are also statistically significant. Any biomedical significance of such differences requires further scrutiny. © Halberg.

**Historical China: cradle of magnetism.** The concerns of chronobiology and magnetics were linked and met, probably before a magnet ever served in the pursuit of an enemy. The Chinese emperor Hoang-Ti had a chariot upon which stood the diminutive figure of a man with an arm outstretched. This figure was free to revolve around its axis, yet the arm always pointed to the south, the direction in which a rebellious tributary prince had fled. The movable figure may have been activated by a magnet, which by 2634 BC may have served in warfare and later became indispensable for navigation. Shon-Kua, a Chinese encyclopedist (1030–93 ad), authenticated in writing the myth about the magnet pointing (north/south) (62).

**Greece and the Middle East.** The scholarship of the late Jürgen Aschoff suggested that the history of rhythm research began 650 years before Christ, when the Greek lyric poet Archilochus of Paros, “a very dynamic person as you will expect from someone who is interested in rhythms” (1), wrote “Recognize which rhythm governs man”. Aschoff did not comment on another fragment by Archilochus, written when he witnessed a solar eclipse (on April 6, 647 BC) (64). The latter fragment reveals that Archilochus was sufficiently interested to note in verse that the eclipse “made night from mid-day, hiding the light of the shining Sun”. This latter fragment authenticates the contribution in the fragment on rhythm as dating from the 7th century BC, and identifies Archilochus as a lyric link, not only to the study of rhythms, but also to that of the sun if not

the galaxies, and to their visible, as well as their subtler but no less important effects. In this perspective, different fragments from the same poet link rhythms, the broader chronobiology, and the transdisciplinary mapping of time structures, or chronomes, to space physics.

During the fourth century bc, the opening by day and closing by night of the leaves of the tamarind tree (*Tamarindus indicus*) was described as the “nyktitropic movement” (now nyctinasty). Hugo Bretzl of Göttingen in 1903 (28) refers to AndrostheneS of Thasos, who in 324 bc commanded a ship with 30 oars in the campaigns of Alexander the Great, explored Bahrain and its flora and the Arabian coast, and circumnavigated India. His book, now apparently lost, was cited by Theophrastus (26). To Bretzl,

AndrostheneS was the lucky one who ... discovered for the first time the important fact that plants are capable of movement, a characteristic previously attributed only to the animal world. Like all scientific observations which were ordered by Alexander the Great himself, the description of the daily periodic [italics Bretzl’s] movements of the leaflets in their four stages is written so clearly and so succinctly that until the time of our new physiological works, it remains the best (description) of the sleep of plants, even if they are not noted and forgotten, as a historical review will describe.

The daily changes from light to darkness rather than those in environmental temperature were imputed by AndrostheneS as the environmental factor to which the plant may respond by the “nyktitropic” movements of its leaves (28). Light-sensitive molecules, photoreceptors, indeed are identified today as intermediates between the aspect of the environment and the plant’s or animal’s circadian system (65). But they may not be the entire story: light is an important “switch” (16, 34, 35, 66, 67), but not the only pertinent cyclic factor (33).

Aschoff’s gallery of ancestors in the study of rhythms includes Hippocrates, Aristotle and, in particular, Galen. He does not, however, mention Avicenna, who found, as had Hippocrates and Galen before him, that the week was an important unit of biological time, usually elapsing between the start and resolution of disease. Thus it was recognized even in antiquity that the circaseptan (about 1-week) interval is built into us (68, 69) rather than being merely a reactive adjustment to a single stimulus that carries no 7-day information, such as a transplant (70), a stay in a spa (69), or the removal of a kidney (71). The latter proposition is supported by a scholarly book by the late Gunther Hildebrandt (69; cf. 72).

**A physician’s treatise on geomagnetism continues tearing down disciplinary barriers.** Geomagnetism took a relatively early formal lead in 1600 due to William Gilbert (1544–1603) (73). Gilbert studied medicine at Cambridge University and set up practice in London; he became president of the College of Physicians in 1599, while he also experimentally documented geomagnetism in his still-famous treatise “De Magnete”. Gilbert also coined the word “electricity”, from the Greek for “amber”, and apparently first distinguished electric from magnetic phenomena.

For each of their two classic volumes on “Geomagnetism”, Sydney Chapman and Julius Bartels (62) use as their motto Gilbert’s “*Magnus magnes ipse est globus terrestris*”. Chapman and Bartels the physicists describe the contribution of Gilbert as “... the fruit of long years of thought and experiment [by] an amateur in physical science [sic], for his profession was medical; in this also, he rose to eminence, being appointed in 1601 chief physician in personal attendance on Queen Elizabeth [I; and thereafter of King James I]. ... His book has been described as the first modern scientific treatise.” Thereafter, Chapman

and Bartels provide an index of chapters, which reveals that chapter 15 of book 1 deals with “the medicinal virtue of iron”. Thus by 1600, the crossing and removal of disciplinary barriers, started much earlier by Androsthene for Alexander the Great, from military science to plant physiology, had led to the crossing from medicine to physics by *the* pioneering treatise of physics as the contribution of a physician. Gilbert’s book is thus a monument for transdisciplinary endeavors.

**Physiological monitoring starts in the 17th century.** Gilbert’s book preceded by only a few years the other major milestone in transdisciplinary science. In 1603, William Harvey noted: “The movement of blood occurs constantly in a circular manner and is the result of the beating of the heart” (74). Also contemporary to Gilbert was Santorio Santorio, who kept a 30-year record of his bodily functions (75). Also in the seventeenth century, Thomas Sydenham (1624–1689), credited with the discovery of the first effective drug for a specific disorder—“Peruvian bark”, whose active ingredient was quinine—advocated the administration of opiates with a specific timing for the treatment of pain, in the evening (76–78). With a few notable exceptions, as in the case of the electrocardiogram, heart rate, blood pressure, temperature and activity, but not yet as a routine, except perhaps for blood sugar in patients with severe diabetes, Santorio’s self-monitoring or Sydenham’s and Virey’s timing (77) still await entry into biomedicine. In most aspects of treatment, Sydenham’s recommendation of what books one should read to qualify as a physician remains timely. In one interpretation, Sydenham’s advice was that whether one reads Cervantes or Hippocrates, one would be equally unqualified for (medical) practice, and equally unsuccessful in it. Cervantes would still be timely in the third millennium AD if one sought for ways of utilizing the normal range of physiological function for health care, in any one of the modern textbooks of pharmacology, physiology or internal medicine. The change from a single sample to a monitoring endeavor (read: chronomics) remains our challenge.

**A missed opportunity in the eighteenth century.** Transdisciplinary activity beyond military science was encouraged by Alexander the Great and extended to plant physiology by his ship’s captain Androsthene. The physician Gilbert followed suit. Thereafter, it was reciprocated as a contribution to biomedicine by the physicist Jean-Jacques Dortous de Mairan (1678–1771), a towering figure in eighteenth-century science (79). Born into the minor nobility, orphaned at sixteen and lacking a complete formal education, he won the Bordeaux Academy of Science’s prize in three consecutive years at a relatively early age, before being asked not to apply again but to become a member. He studied physics and mathematics, among other fields, in Paris from 1698–1702, and became a professional astronomer (79) who wrote about a variety of topics in physics and became perpetual secretary of the French Academy of Science.

De Mairan reported incidentally that he moved a “sensitive” heliotrope plant (perhaps *Mimosa pudica*) to a place where sunlight could not reach it. He found that the plant still opened its leaves during the day and folded them during the

night (27). His finding can be interpreted as demonstrating the persistence of what we now call circadian rhythms (80). It seems noteworthy that the circadian rhythm continued in the very absence of the daily change in light and darkness (and, we add), interpreted as the cause of nyctinasty by Androsthene. Credit is due to de Mairan for this finding as such. He deserves even greater credit for adding that the persisting rhythm was not only endogenous, but also of interest to medicine. De Mairan concluded, however, that it was not his job to pursue the problem<sup>2</sup>. This line of thought, in a different contemporary context, is rightly criticized by Juan Roederer (81), who as a physicist cites Georg Christoph Lichtenburg’s (1742–1799) aphorism, equally apropos of other sciences: “He who understands nothing but chemistry does not fully understand chemistry either”.

Erwin Bünning (82) had the scholarship to find de Mairan’s physiological contribution (27) and to interpret the observation on the plant from a “clock” viewpoint. He may have been unaware or unimpressed by de Mairan’s interest in the aurora, and suggested, as have many others, that the sensitive plant continued nyctinasty “... in the absence of environmental time cues ...”. Apparently not stated, or perhaps not known by scholars in the field of clocks, is the fact that de Mairan, as a physicist, wrote specifically on the topic (including the history) of the aurora borealis, the northern lights that coincide with magnetic storms and occur primarily around the magnetic poles, prominently visible with the naked eye by night, the auroras themselves thus undergoing a “circadian” appearance.

Without scrutiny or even knowledge of de Mairan’s book on the aurora borealis<sup>3</sup>, it would have seemed tempting to speculate that he may have suspected geomagnetics as possibly providing a 24-hourly periodic signal for the sleep movements of the sensitive plant kept in continuous darkness, an as-yet unsolved problem. In looking into de Mairan’s history, the senior author was lucky in several ways. He tracked down a micro-card copy of de Mairan’s book (79), painstakingly reading it page by page under a magnifying viewer, until he found the buried statement that de Mairan ruled out *magnetism as the phenomenon underlying the aurora borealis*. It was disappointing to read that he had indeed considered the possibility that geomagnetics contributed to auroras (if not to the sleep of plants) but ruled it out because he believed that “magnetic material is constant”. This is the more regrettable since de Mairan deserves further credit for identifying the role of “particles from the sun” being involved in the aurora (centuries before a solar wind was identified).

De Mairan refers to Descartes, to whom it occurred to consider a solar atmosphere consisting of very rarefied matter, which he called “air”, comparable to the air that surrounds our earth; he supposed it to extend from the sun, to the sphere of Mercury and even beyond, and ascribed to it a similar origin. What appears to favor this idea is that for the last 5 or 6 years (i.e., the maximum half of the 11-year cycle, adds Schove [83]), the aurorae, as often happens, have become very frequent, and, according to our (de Mairan’s) hypothesis, should

2. *Errare humanum est*: de Mairan did not reciprocate Gilbert’s gift to physics, but rather set a (bad) precedent for the many “isolationist” physicists who wish to adhere to their disciplinary barriers. The latter correspond to biologists who refrain from implementing their job, which includes the interpretation of rhythms outside and inside us and the relations among them.

For instance, an increase in myocardial infarctions can be associated with magnetic storms in space, in some solar cycles and/or in some of their stages (33). But many problems remain to be clarified by coordinated transdisciplinary cooperation by physicists and biologists before any undesirable effects will eventually be prevented by countermeasures and possibly desir-

able effects enhanced. Neither will be implemented before disciplinary barriers are crossed. To paraphrase the original *Errare humanum est; perseverare diabolicum* for today’s physiologists and biologists alike, *perseverare in errore non est laudabile*.

3. As may have been the case for most biologists or historians citing de Mairan.

be associated with great extensions of this air (*italics in original*), which have likewise been numerous (83). Schove points out further that de Mairan emphasized *the frequency* of aurorae and sunspots in the early seventeenth century, until the 1620s, and their rarity in the period from 1650 to 1670 (83).

Having postulated that particles from the sun may reach the polar regions, de Mairan could also have postulated and checked whether the timing of the rhythm in leaf movement persisting in continuous darkness may have been synchronized by 24-hourly changes in geomagnetic intensity or disturbance. Had he measured the latter, a task in his very field of physics and near to the major goal assigned to him by his academy, to clarify the mechanism of the aurora, he would have discovered as a minimum that magnetic material is not constant (79). In other words, de Mairan could have changed his attitude that he must not follow-up on something outside his field, and could have concurrently pursued both the sleep of plants and the physical problem of the aurora borealis. In so doing, he might have unquestionably improved at least the interpretation of his own topic. Whether or not there is possibly also a subtle association between geomagnetics and the sleep-movement of plants requires further study. Rather than assuming constancy, de Mairan would have discovered geomagnetic periodicity in any event, i.e., the changes along the 24-hour scale in terrestrial magnetism, as did eventually François Arago (1786–1853) in 1827, according to a letter by Humboldt to Gauss (10). The test of the speculation whether geomagnetic changes relate in any way to the sleep of plants remains a challenge for physicists and plant physiologists alike.

**Arago's 24-h variation of terrestrial magnetism.** Geomagnetic recordings along the 24-h scale are associated with Carl Friedrich Gauss (1777–1855) and Wilhelm Weber (1804–91), who described the variation along the 24-h scale in terrestrial magnetism at different latitudes in Europe as a “harmony of curves”, Figure 7 (84; cf. 85). The correspondence of Alexander von Humboldt (1769–1859) and Gauss indicates, however, that Arago made findings that antedate Gauss’ initiative, specifically in tracking 24-h variations in magnetism. On Feb. 2, 1833, Humboldt wrote to Gauss that he had found a Dec. 13, 1827 letter from Arago. Arago had resumed his observations on magnetism along the 24-h scale with a new method and had found [as cited in Arago’s words by Humboldt to Gauss] “... *each day* a regular variation. The inclination is greater at 9 a.m. than at 6 p.m. ... [T]he intensity measured by a horizontal needle, by contrast, is at its minimum at the former time, and that it obtains its maximum between 6 and 7 p.m. ... [O]ne could suppose that it is due but to a sole change in inclination, and in effect the greatest portion of the apparent *variation of intensity* depends on the daily diurnal alteration of the horizontal component ... [T]here nonetheless remains a small quantity as an index of a *real variation of intensity*.”

Humboldt in turn was interested in sudden fluctuations of the earth’s geomagnetic field, the so-called magnetic storms that he encountered by measurements made in his Berlin garden. “To discover whether these magnetic storms were of terrestrial or extraterrestrial origin”, he proposed “a worldwide net of magnetic observatories”, which he then advocated at the Royal Society in 1836. Arago’s letter to Humboldt con-

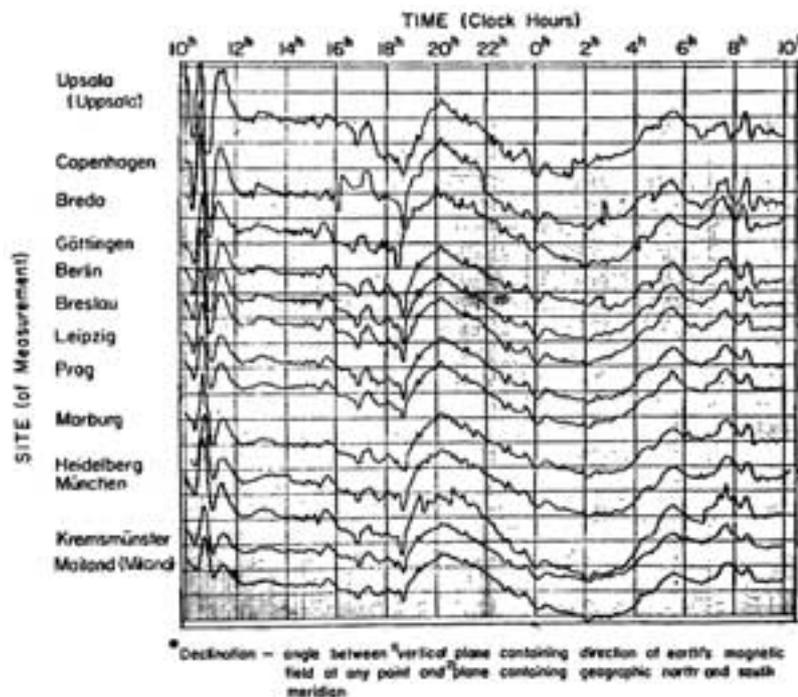


Fig. 7. The “harmony of curves” in itself can definitively be documented (but not quantified) in instances such as this record presented without any inferential statistics by the discoverer of the least-squares method, Carl Friedrich Gauss, with Wilhelm Weber (84).

veys the excitement of the physicist who experienced “real” changes along the 24-h scale. Admittedly, we do not yet know whether the movement of Arago’s Gambey needle was temperature-compensated (86). Others in biology felt the same excitement when they found circadian rhythms to differ among inbred strains, to be ubiquitous, and to make the difference between death and survival in response to an identical stimulus (87; cf. 16). The association of geomagnetics with biodata is documented thus far in the infradian spectral domain (33, 88).

**Intellectual climate regarding periodicity and barrier crossing from pharmacy and botany to astronomy.** Shortly after 1600, the telescope was invented, and Galileo, Scheiner, Harriot, Fabricius and eventually Newton began observing sunspots. But the discovery of the about 11-yearly (circadecennian, or briefly circadecennian) periodicity awaited the trained pharmacist and amateur botanist/astronomer Samuel Heinrich Schwabe to cross disciplinary barriers in the nineteenth century (88, 89), repeating the feat of another amateur botanist, Androsthene. While Schwabe, in counting sunspots, did not dare to extrapolate to the importance of the solar activity cycle on earth, and indeed, while conclusions must not be drawn from the finding of variations with similar periods, it is nonetheless most interesting that in the very year 1838, when Schwabe published the first 12 years of his observations (88), without even daring suggest a cycle in the face of an obvious up-and-down trend, Clarke described an about 10- to 11-year trade cycle (90; cf. 83, 91). Revolutions and the climate as well as the economy were then already related to solar activity (83): in 1801, William Herschel had described the weather as subject to a “solar indisposition” (92; cf. 83).

M.J. Johnson, the president of the Royal Astronomical Society, said in his address on presenting the Society’s medal to Samuel Heinrich Schwabe in 1857 (93; cf. 94):

M. Schwabe is a gentleman resident in ... Dessau, the capital of the Duchy of Anhalt Dessau, who, having no professional duties, has devoted much time and attention to scientific studies, and has attained considerable reputation in other departments of knowledge than that in which he is known to this Society. Among other accomplishments, I am informed that M. Schwabe is an excellent botanist, and has composed, though, I believe, not published, a flora of the neighbourhood of Dessau.

It was in 1826 that he entered upon those researches which are now to engage our attention. I am not aware of the motive that induced him<sup>4</sup>—whether any particular views had suggested themselves to his own mind—or whether it was a general desire of investigating, more

thoroughly than his predecessors had done, the laws of a remarkable phenomenon, which it had long been the fashion to neglect. [Author's note: He did a pointed description of the view that periodic phenomena were not profitable to study, perhaps conveying the thought of all those who seek solutions, mathematical or biomedical, without accounting for time.] He could hardly have anticipated the kind of result at which he has arrived; at the same time we cannot imagine a course of proceeding better calculated for its detection, even if his mind had been prepared for it, than that which he has pursued from the very commencement of his career. Assuredly if he entertained such an idea, it was not borrowed from the authorities of the last century [author's note: including Galileo and Newton], to whom the solar spots were objects of more attention than they have been of late years.

"Nulla constanti temporum lege apparent aut evanescent," says Keill in 1739. — *Introduct. ad. Physic. Astronom.* p. 253.

"Il est manifest par ce que nous venons de rapporter qu'il n'y a point de règle certaine de leur formation, ni de leur nombre et de leur figure," says Cassini II. in 1740. — *Elém. d'Astron.* vol. i, p. 82.

"Il semble qu'elles ne suivent aucune loi dans leur apparitions," says Le Monnier in 1746. — *Instit. Astron.* p. 83.

"Solar spots observe no regularity in their shape, magnitude, number, or in the time of their appearance or continuance," says Long in 1764. — *Astron.* vol. ii., p. 472.

"Les apparitions des tâches du soleil n'ont rien de regulier," says Lalande in 1771. — *Astron.*, vol. iii, § 3131, 2d edit.

And Delambre's opinion may be inferred from a well-known passage in the third volume of his *Astronomy* (p. 20), published in 1814, where treating of the solar spots he says, "Il est vrai qu'elles sont plus curieuses que vraiment utiles."

I cite these passages to show, whatever might have been Schwabe's own view of the matter, that a periodicity of the spots was not a current idea at the time he entered upon the subject, and therefore that he has not merely developed a law for which men's minds were prepared, but that he has been, to all intents and purposes, the discoverer of it. The first suggestion I have met with (and that a very vague one) of anything of the kind occurs in the article "Sonnenflecken", in Gehler's *Physikalisches Wörterbuch*, written by the elder Littrow, and published in 1836, long after Schwabe had been at work.

It was in 1826, as I have said, that Schwabe began his observations, but I am not aware of any published results before those in No. 350 of the *Astronomische Nachrichten*, which appeared in April 1838. Here he gives a summary of twelve years' labour, and though at this time he must have begun to foresee the issue, for the indications of periodicity are plain, he makes no remark, nor does the memoir appear to have attracted the attention of astronomers.

From this time commence his annual contributions to the *Astronomische Nachrichten*; but it was not until the end of 1843, when he had passed through two periods of maximum and minimum, that he very modestly remarks that his observations heretofore had given indications of periodicity which that year's result tended to confirm. Still the subject attracted little attention. As far as I can discover, the only person who had taken it up was Julius Schmidt, the present indefatigable Director of the Observatory at Olmütz, then residing near Hamburg. But the philosopher of Dessau was not disconcerted; he went on accumulating fresh proofs of his great discovery, which, when announced in 1851, by Alexander Von Humboldt in the third volume of his immortal *Cosmos*, came upon the world with all the freshness of novelty, though in reality the secret had been revealed eight years before. ... His observatory, I am informed by Mr. Carrington, is a small apartment on the top of his dwelling-house. ...

The exact period Schwabe does not pretend to have determined. That it is liable to perturbation is evident. During twenty-seven years of the series the results were extremely regular; during the last three years they have shown symptoms of disturbance. The epoch of minimum, which, consistently with earlier indications, should have happened in 1853, did not occur until 1856. ...

There is, however, one more topic too closely connected with our subject, and too remarkable to pass unnoticed.

You are aware, gentlemen, it has been long known that the intensity of magnetic declination is subject to a daily variation; and this variation was also known to be in some way connected with the sun, attaining its maximum western limit when that body is at its upper and lower culmination, and its maximum eastern limit about 6 o'clock in the morning and evening. These are not the exact times, but they are sufficiently near for our purpose. About the year 1850, Professor Lamont announced that this variation was again liable to another variation, which observed a period, from maximum to minimum, and from minimum to maximum, of about 10 years. He was led to this result by a discussion of his own observations at Munich. It was shortly after fully confirmed by our colleague, General Sabine, by the observations made at the Magnetic Observatories of Toronto and Hobarton. But in the course of the latter discussions General Sabine detected another important circumstance which had escaped Lamont, viz., that the periods of maximum variation of the declination-needle corresponded exactly with those of the maximum frequency of the solar spots, and *vice versa*, the minimum of the one with the minimum of the other. Hardly had General Sabine's paper been read before the Royal Society on March 18, 1852, when intelligence was received that two Swiss physicists, Professor Gautier of Geneva, and Professor Wolf of Berne, had arrived at the same conclusion, independently of each other, from a perusal of Lamont's results.

All the observations I have mentioned, were made during nearly the same time—between the years 1840 and 1851—comprehending only a single period of change. Obviously, therefore, in this state of the inquiry it was of the highest importance to obtain a trustworthy series made at another time and under different circumstances. Though hardly to be expected, it happened, most fortunately, that such a series was at hand.

The diurnal variation was one of those subjects which, many years ago, had particularly interested the vigorous mind of the lamented Arago; and among his papers were found the records of a most laborious course of experiments, conducted with all the care which no one knew better than he how to bestow on a delicate investigation. These experiments, extending from 1820 to 1831, have been rigorously discussed by M. Thoman, and exhibit the prevalence of the same law that obtains in the later series.

Nor does the evidence of connexion rest here. In a recent paper sent to the Royal Society, General Sabine has shown that at Toronto (the only series hitherto fully discussed) all the magnetic elements subjected to observation undergo similar variations. In the face of these coincidences, to doubt the relationship between the two phenomena seems to me to be almost as unreasonable as to doubt the influence of the moon on the tides of the ocean.

M. Schwabe's service has been the discovery of an important astronomical fact, falling strictly within the cognizance of this Society. His merits are in no way affected, though, no doubt, the value of his discovery is enhanced, by this remarkable episode. No longer is its scope confined to the disclosure of a physical peculiarity in the constitution of the sun. It promises to be the means of revealing the prevalence of a principle, throughout the solar system, co-extensive with gravitation, and of establishing another link in the chain of analogies binding Earth with other worlds, the ultimate effect of which on the progress of physical research no one can foresee.

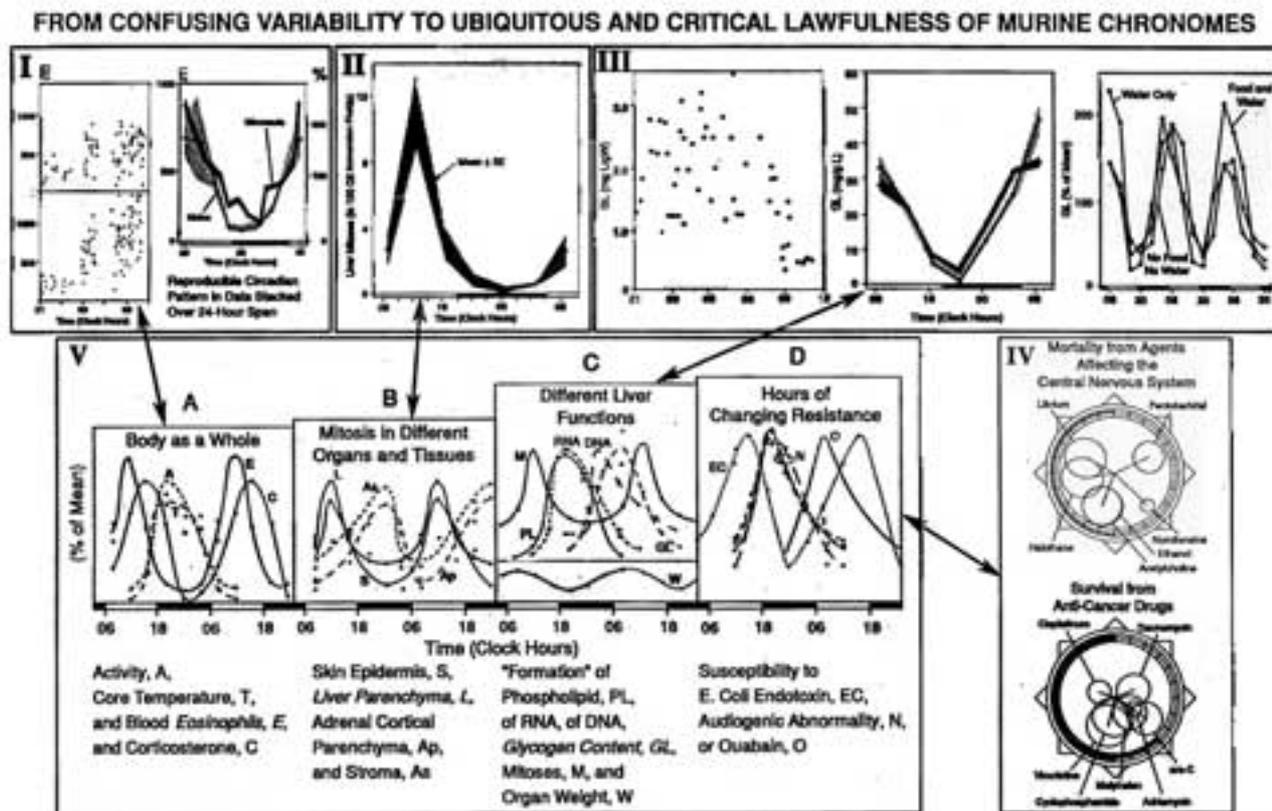
\*

**Minnesotan developments.** *Si parva licet componere magnis*, the senior author never saw in biology the nearly perfect parallelism of curves of Gauss and Weber in Figure 7, which he had reproduced for a meeting of physicists in 1969 (85). He was then unaware of Humboldt's letter to Gauss (10) and of Johnson's remarks describing Arago's priority (93). But over half a century ago, he shared the excitement with which Arago informed Humboldt of a diurnal variation when he counted blood eosinophils of mice (87; cf. 16). A very great variability, shown in

4. In a letter to Carrington of the Royal Astronomical Society (94), Schwabe wrote (that his observations were not hypothesis-driven, but rather) that he eventually became interested because "the sunspots [if not the mountain] were there". He mentioned that his friend Harding of Göttingen wrote to me that there was a great want of physical observations of the sun, that the subject presented an almost unworked

field, and that labour therein might be rewarded by the discovery of a planet interior to Mercury. The communications of Harding and of a friend in Berlin led me also to inquire into the rotation of the sun, in which I found some difficulty from the instability of the spots. Nevertheless, I convinced myself that the opinion of Schroeter, that the spots had an independent motion, was unfounded, and that the apparent movement

was attributable rather to the enlarging of one side and the filling in of the other side of a nuclear spot, whereby the estimated centre was shifted. My enumerations, however, early led me to notice a tolerably regular increase and decrease in the number of the spots, so that I may compare myself to Saul, who went out to seek his father's asses, and found a kingdom.



**Fig. 8.** Time plots of original values (dots) of variables such as blood eosinophils (E) (I, left) or glycogen content (III, left) reveal great variability, confusing at first, until the data are processed by relatively simple statistical techniques such as averaging and stacking over an idealized 24-hour span corresponding to an anticipated periodicity. Once this is done and the results are displayed as a function of time, they show the time-macroscopic ubiquity of circadians. The averaging of data obtained during different hours of the day also reveals differences in the time course (in phase) of different functions of a given organ such as the liver (VC), of cell division (mitosis) in different organs and tissues (VB) and of different variables in the body as a whole (VA and D). The structure of the circadian system becomes apparent by the application of the methods of chronobiometry: the circadian variation in blood eosinophils determined years apart in two laboratories as far apart as Minnesota and Maine is reproduced (I, right). The lawfulness of the circadian variation yielded by the application of chronobiologic techniques is also revealed for the drastic changes in liver glycogen content (III, middle). In this case, a circadian rhythm

in the liver's glycogen is seen to persist under conditions of starvation and dehydration, with little if any alteration in the dynamic rhythm characteristics, as compared to usual *ad lib* conditions, once the data are expressed as a percentage of the overall mean (III, right). After a prominent circadian rhythmicity was found at different levels of organization, several series of experiments were carried out under rigorously standardized laboratory conditions in order to investigate the effect of a single physical stimulus such as exposure to noise. Outcomes were as different as no response, convulsion or even death, as a function of the circadian stage at which the organism was exposed to noise. Whether the stimulus was audiogenic or the exposure to an endotoxin, or to a drug such as ouabain, or to whole-body irradiation, predictable changes were found as a function of the circadian stage at which the stimulus was applied, albeit with differences in the timing of these susceptibility-resistance rhythms to different agents. The *hours of changing resistance* were thus uncov-

ered, and the times of overall largest response by the organism to a fixed stimulus applied at different rhythm stages mapped (VD). Applications followed (IV). Prominent susceptibility rhythms were documented in the experimental laboratory, as illustrated here for the case of the mortality from agents affecting the central nervous system and for the case of the survival from (tolerance of) toxic doses of anticancer drugs. In each case, the nonoverlap by the elliptical 95% confidence region of the center of the circular plot (pole) can be interpreted as the presence of a statistically significant circadian rhythm in the susceptibility of the organism to each of these different agents. The orientation of the directed line (vector) indicates the time of acrophase, that is the time of the largest anticipated response. Such charts are helpful in guiding the timing of the administration of the various agents so mapped. The chronotherapy of cancer is one critical application resulting from this work. © Halberg.

Figure 8, on the left of Section I, had to be averaged before lawfulness emerged in Minnesota (87, 95) and was confirmed in Maine (96), in the right-hand panel of the same section. These observations were then extended to a plethora of findings in Figure 8 and elsewhere (30) during the second half of the twentieth century that led to the start of the quantitative inferential statistical science of chronobiology (16). Numerical near-matches of the period of the previously known rest/activity and sleep/wakefulness rhythms were found at all levels of organization. What came to be known as a circadian rhythm, with a free-running period, was detected even at the level of mammalian nucleic acid formation (34, 35, 97).

At the time the findings were made, this was considered revolutionary, since DNA was held to be the most invariable material inherited from generation to generation. It was used as the presumably unchanging, constant chemical reference

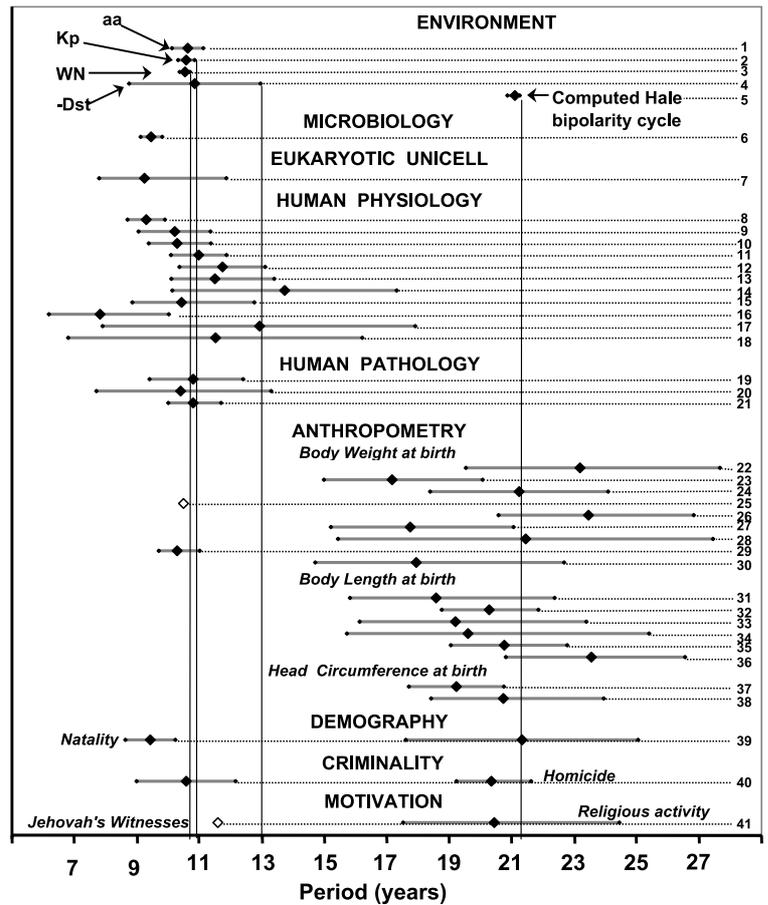
standard to which the results of other chemical determinations were related. In the 1950s, the late Prof. Cyrus P. Barnum was the leading Minnesotan biochemist interested in RNA and DNA. He felt he could not justify providing the time of a government-funded technician for a test of the unorthodox possibility that nucleic acid formation underwent a 24-hour rhythm; nonetheless, he was so intrigued that he became the tech himself. It was equally revolutionary by 1960 to document circadians in bacteria (25). A confirmation in the 1970s notwithstanding (98), circadians in prokaryotes were still denied by an entire committee two years later (99). It took until the 1980s before they were accepted as ubiquitous (100–105).

Even more surprising than the ubiquity of circadians was the importance of these heretofore vexing, confounding “diurnal variations”. The circadians proved to be a critical, seem-

ingly universal design feature; they accounted for the difference between life and death in response to the same stimulus, whether physical, such as noise (106, 107) or X-ray radiation (108, 109); biological like an endotoxin (110), or a long list of anti-cancer and other drugs (111–115). Timing made the difference. The importance of timing was then extended to the biological week (72). An about 7-day (circaseptan) pattern contributed to the difference between the stimulation and inhibition of a malignant growth (116, 117). Eventually, an ever broader spectrum of biologically new and relevant rhythms was mapped (16, 17, 118). New frequencies in many kinds of time series were revealed. Intermodulations occurred at several frequencies within the spectral structure of a variable; interactions were also mapped among variables in us and further as interactions (documented by cross-spectral coherence away from spectral peaks) among cycles in and around us (32, 33, 37). These cycles organized deterministic chaos and were subject to trends, and the three elements, rhythms, trends and chaos, were recognized as part of a physiological time structure. Concomitantly with these quantitative inferential statistical steps, and for millennia before them, a descriptive but neither quantitative nor inferential time-macroscopic background developed at the behavioral level.

*Time structures: chronomes.* Whenever the density and length of the time series permits, chronobiologists today can engage in mapping more and more complete chronomes. Chronomics focus on deterministic (and any other) chaos as one element, whenever the time series is dense enough and its nonlinearity can be documented (119–121). Trends constitute another element. Both chaos and trends may coexist with a third critical spectral element of rhythms with widely varying cycle lengths, now covering a scale of ~12 orders of magnitude from electrical discharges (e.g., around 500 Hz or 0.002 s in electrical fishes and around 50 Hz or 0.02 s in human EEG) to infraannual (multi-)decadal cycles (e.g., around 50-year or ~6.10<sup>-10</sup> Hz cycle in homicides) in now-living individuals and populations (Figure 9 and Table 1), with reportedly repeated extinctions during a much longer trend in evolution. An organism's chronomes intermodulate with the spectral elements of external socio-ecological chronomes, including components of electromagnetic and biological spectra. Some components, like the highly variable geomagnetic near-week of ~6.75 days on the average, when over 50 (37) or over 100 years of data (122) of  $K_p$  and *aa*, respectively, are used, were found first (37; cf. 33) because of their biological counterpart (16, 68). The Sunday or weekend phenomenon (63), fully confirmed by us in the data set originally used by Fraser-Smith, changes its shape in the complete, now-available data set. When sections of the entire data set are separately analyzed, there is a Monday or Tuesday or other "phenomenon". It is hardly surprising that it was not found in the Antarctic with conventional analyses (123). When, on the basis of earlier analyses of the planetary index  $K_p$  (37) and confirmatory evidence (122), 2 years of data from a stand-alone magnetometer in Antarctica are analyzed, two components stand out, one of ~6.75 days being numerically larger than the other with a period

**CHRONOMICS: CIRCADECENNIANS and CIRCAVIGINTENNIANS  
( ~10.5- and ~21-YEAR CYCLES AROUND and IN ORGANISMS )**



**Fig. 9.** Mapping of about 10.5- and 21.0-year cycles in biology, aligned with similar cycles in natural environmental variables. For detailed information of each data series see Table 1. Results presented as point and 95% confidence limits derived from linear-nonlinear rhythmometric analyses. An about 21-year component can also be validated for the antipodal geomagnetic index *aa* when data over a 130-year span are considered. © Halberg.

of precisely 7 days (124). The former is likely the natural physical feature and the latter, perhaps, an indicator of human-made global pollution. The difference between these two components was computed by Dewayne Hillman for sections of the available >133 years of data on the *aa* index and thus a change in sign of the difference was demonstrated with statistical significance (cf. 124). Hufeland deserves credit for having singled out the 24-hour period as a basic unit of our make-up in time (125). But the scope of chronomics is much broader, Figure 10.

Circadian system physiology can aim to be precise at all levels, including the molecular (126). In the context of "reducing time" (126), chronobiology is like a yardstick with one end cut off. It may still be precise in measuring inches; but if one mistakes the remaining length of the stick for one yard, one may be greatly inaccurate in measuring lengths much greater than that of the stick, Life lasts longer than one day, and at any moment in time, one is under the influence of cycles much longer than one day. To extend the analogy of the intact yardstick, chronomics aims to be accurate in the measurement of the length of all periodicities and of other elements of chronomes. Thanks to genetic coding, we assess, in the biological chronomes, a complex spectral element that through phylogeny and ontogeny may replay solar-terrestrial history for several billion years (37). The systematic recording of physical variables, such as light, temperature, atmospheric pressure, geomagnetic disturbance on earth, and of sun-related and other variables from vehicles in space, is as yet unmatched in biomedicine. The biological chronomes now being mapped include circadian and circannual

		Some circadecennian and circavigintennian cycles in and around us							
Line		Period (years)			Series duration Dates	Number Years	Number of data	Geographic site	
		Lower limit*	Best Fit	Upper limit*					
<b>Environment</b>	1	aa = Antipodal Geomagnetic Index	10,12	<b>10,63</b>	11,13	1890-1999	110	1 / year	
	2	Kp = Planetary Geomagnetic disturbance	10,32	<b>10,58</b>	10,85	1932-1999	68	1 / month	
	3	WN = Wolf relative sunspot number	10,37	<b>10,54</b>	10,70	1890-1999	110	1 / year	
	4	-Dst = Equatorial geomagnetic disturbance	8,75	<b>10,85</b>	12,96	1973-1999	27	1 / year	
	5	Bipolarity "Hale Cycle" **	10,48	<b>10,51</b>	10,55	1700-1999	300	1 / year	
			20,86	<b>21,10</b>	21,26	1890-1999	110	1 / year	
			21,42	<b>21,428</b>	21,43	1700-1999	300	1 / year	
<b>Biology</b>	6	Prokaryotes: Air Bacterial Sectoring	9,12	<b>9,45</b>	9,81	1970-1982	13	3 744	Italy
	7	Eukaryotes: Unicellular Algal O <sub>2</sub> Production	7,79	<b>9,24</b>	11,87	1980-1991	11	324	Germany
<b>Physiology***</b>	8	Mood (RBS)	10,11	<b>11,50</b>	13,41	1966-1998	33	~5 / day	USA
	9	Time (1-Minute) Estimation (RBS)	9,38	<b>10,29</b>	11,37	1966-1998	33	~5 / day	USA
	10	Urinary 17-ketosteroid excretion (CH)	8,70	<b>9,30</b>	9,90	1948-1963	15	1 / day	Denmark
	11	Peak Expiratory Flow (RBS)	10,36	<b>11,74</b>	13,11	1966-1998	33	~5 / day	USA
	12	Respiratory Rate (RBS)	10,13	<b>12,50</b>	17,32	1966-1998	33	~5 / day	USA
	13	Systolic Blood Pressure - SBP (YW)	9,05	<b>10,21</b>	11,36	1966-1998	33	~5 / day	USA
	14	Standard Deviation of SBP (YW)	8,85	<b>10,43</b>	12,76	1987-1998	11	~48 / day	Japan
	15	Diastolic Blood Pressure - DBP (YW)	10,09	<b>10,98</b>	11,87	1966-1998	33	~5 / day	USA
	16	Standard Deviation of DBP (YW)	6,18	<b>7,82</b>	10,02	1987-1998	11	~48 / day	Japan
	17	HR (YW)	9,54	<b>12,93</b>	17,91	1987-1998	11	~48 / day	Japan
	18	Standard Deviation of HR (YW)	8,27	<b>11,52</b>	16,22	1987-1998	11	~48 / day	Japan
<b>Pathology</b>	19	Myocardial Infarctio	10,00	<b>10,80</b>	11,70	1960-1996	37	129 205	USA
	20	Leptospirosis	9,40	<b>10,80</b>	12,40	1949-1995	47	2 907	Slovakia
	21	Diabetes	7,70	<b>10,40</b>	13,30	1985-1995	11	1 369	Slovakia
<b>Anthropometry</b>		<b>Body Weight</b>							
	22	Boys Minnesota	19,53	<b>23,19</b>	27,67	1963-1998	36	2 136 745	USA
<b>at birth</b>	23	Alma-Ata Russians	14,99	<b>17,17</b>	20,07	1946-1998	53	9 056	Kazakhstan
	24	" Kazakhs	18,39	<b>21,24</b>	24,05	1946-1998	53	3 459	Kazakhstan
	25	Moscow		<b>10,49</b>		1874-1985	112	5 987	Russia
		<b>Girls</b>							
	26	Minnesota	20,58	<b>23,46</b>	26,83	1963-1998	36	1 039 464	USA
	27	Alma-Ata Russians	15,21	<b>17,75</b>	21,06	1946-1998	53	9 105	Kazakhstan
	28	" Kazakhs	15,44	<b>21,45</b>	27,45	1946-1998	53	3 448	Kazakhstan
	29	Moscow	9,70	<b>10,29</b>	11,01	1874-1985	112	5 840	Russia
		<b>Both genders</b>							
	30	Denmark	14,71	<b>17,94</b>	22,68	1973-1994	22	1 166 206	Denmark
		<b>Body Length</b>							
		<b>Boys</b>							
	31	Alma-Ata Russians	15,82	<b>18,58</b>	22,38	1946-1998	53	9 026	Kazakhstan
	32	Moscow	18,76	<b>20,28</b>	21,86	1874-1985	112	5 976	Russia
		<b>Girls</b>							
	33	Alma-Ata Russians	16,13	<b>19,20</b>	23,39	1946-1998	53	9 105	Kazakhstan
	34	" Kazakhs	15,72	<b>19,60</b>	25,40	1946-1998	53	3 485	Kazakhstan
	35	Moscow	19,05	<b>20,76</b>	22,78	1874-1985	112	5 976	Russia
		<b>Both genders</b>							
	36	Denmark	20,81	<b>23,55</b>	26,55	1973-1994	22	1 166 206	Denmark
	37	Head Circumference Boys Moscow	17,71	<b>19,23</b>	20,75	1874-1985	112	5 976	Russia
	38	Girls "	18,42	<b>20,73</b>	23,95	1874-1985	112	5 820	Russia
<b>Demography</b>	39	Birth rate	8,63	<b>9,43</b>	10,23	1940-1996	57	57	USA
			17,61	<b>21,33</b>	25,05	1940-1996			
<b>Criminality</b>	40	Homicide	8,99	<b>10,58</b>	12,16	1900-1998	99	99	USA
			19,23	<b>20,35</b>	21,62				
<b>Motivation</b>	41	Religious activity of Jehovah's Witnesses	17,52	<b>20,44</b>	24,45	1950-1999	50	328,572 <sup>#</sup> 5,653,987 <sup>###</sup>	Worldwide

\*95% confidence limit. \*\* Computed by changing the sign of WN at each WN minimum. \*\*\*RBS - Dr. R Sothorn, CH - Dr C Hamburger, YW - Dr. Y Watanabe. # at the beginning, ### at the end. SBP & DBP: Systolic & Diastolic Blood Pressure.

systems, approximating in their length the photic and thermic cycles in the environment. These visible or otherwise still obviously grossly sensed, nearly ubiquitous biological near-matches of photic cycles can now be aligned with a partly novel set of physiological rhythms with circa-periods, corresponding mostly to invisible non-photoc environmental cycles. The evolutionary integrations into our environment include periods of about a week, about a month, about a half-year, or about one, about two, or about 5 decades. Chronomics assess these cycles in biology and in the environment, Figure 9 and Table 1. The biological counterparts of invisible, not readily or consciously perceived subtle aspects of a spectrum of natural physical environmental periodicities may be related to past and/or present

corporecular, gravitational and/or other purely physical cycles, of interest in themselves, as in the case of components in the aa spectrum. The probable genetic coding of some of the past cycles, e.g., in geophysical pulsations, has taken us back to the history of magnetism, long before the present day, and the analyses of geomagnetic chronomes may serve to separate human-made pollution from natural cyclic change.

Against this background, a series of analytical and/or interpretative essays about a few individuals, starting with Earl E. Bakken, are intended to provide glimpses of the intellectual climate prevailing at the time of milestone contributions to chronobiology. The essays revolve around how the study of the mechanisms of the body's structure in time—chronobiol-

ogy—developed into the mapping of ever-present time structures, i.e., chronomes, in us and around us. As already noted, for a gallery of chronobiologists, initiated herewith, emphasis is on the living. While death is no exclusion criterion for the gallery in this journal, the authors wish, first and foremost to describe the setting and contributions of those still living, while they can comment, before publication, on how we see them, protest if they disagree, propose changes if they desire, and ascertain that when one memory fails, another may have stored the pertinent circumstances in more detail and perhaps

in a different light. In the pages of this journal, the intended gallery does not presume to be all-inclusive. The *raison d'être* for inclusion is the implication that those selected are relevant to the intellectual climate of chronobiology's splitting the normal range by chronomics, as a step toward one or the other basic or applied goal. Our focus here is on chronomics and applications. Accordingly, we start with an unquestionable contribution in the broader context of restoring the rhythm of the heart (11).

## Earl Elmer BAKKEN: Contributor to and time-witness (*Zeitzeuge*) of chronobiology and now of chronomics

The setting of a few of Earl Bakken's contacts with chronobiology as it developed in Minnesota, and as it now led to chronomes with worldwide cooperation, is described herein. The road to mapping variability — chronomics — is not considered in Earl's own book (11) or in books by others about him (127, 128). Without recognizing the pacemaker as a chronobiologic endeavor, prior books emphasize Bakken, the successful engineer and entrepreneur, but draw no parallels to the likes of Bill Gates, Jim Clark or Ted Turner (129, 130). Herein, we present Earl the scientist who, during the past half-century, contributed directly to humanity in general and to chronobiology and the sciences spawned by this discipline, chronomes in particular:

1. several generations of devices for making the heart beat, restoring the rhythm of the heart. This task will eventually be accomplished in a time-structure-integrated way for which rhythms with a broad spectrum of components, as well as chaos and trends, not only with age but also with disease risk elevation, may well change a purely curative device into a preventive one (14, 15, 131);
2. an early device for rest-activity-based marker rhythmometry on rodents. The device, itself long-lost, is now of interest as a historical concept, translated already into telemetry (132) for laboratory testing of drugs. The technology awaits transfer to humans for timely and timed treatment;
3. an historic concept in chronobiologic modelling, the analogy of a free-running oscillator; and
4. a holistic approach in health care combining high touch with high tech; both are amenable to chronobiologic optimization guided by reference to time structures, chronomes, resolved in the physiological range (133).

**From flannel shirt and jeans to tailor-made suits by way of life-saving devices.** In his memoir, which is truly the story of "One Man's Full Life" (11), Earl describes his "headquarters": when the senior author first met him, it was a railroad box car, enlarged to the size of a three-stall garage (11). As described on the jacket flap, his book is "a candid and plainspoken recounting of an incredibly rich life that began in a blue-collar neighborhood of Minneapolis, blossomed into the labs and offices of the world's leading medical-technology company, and continues to flower in the earthly paradise of Hawaii." Earl has been honored on innumerable occasions for his accomplishments in rehabilitation: for his and his firm's development of a series of invaluable treatment devices, keeping people alive (11, 127, 128). Gradually, he became "Mr. Biotechnology" *par excellence* worldwide. He is also known for his concerns about a broader than device-based holistic health care; in this context, he includes endeavors toward a healing Big Island of Hawaii, centered around a model, award-winning hospital. He is a

recipient of the U.S. National Academy of Engineering's inaugural Russ Prize, created as engineering's answer to the Nobel Prize (134). His past associations with chronobiology and his corresponding perspective for the future have been alluded to by us earlier (131) and in a series of appended published scientific titles.

**Chronomics.** During the past half-century, with Earl, chronobiology in Minnesota started, also quite modestly, with a glimpse of the blood cell dynamics of a few inbred strains of mice (87). The endeavor has become a discipline in its own right (16; cf. 2–5, 17, 18). Its computer methods resolve, around the world, a time-microscopic, including a chromomolecular, make-up in time. A chronobiologic pacemaker would highlight Earl's original feat. The relation of restoring the rhythm of the heart to chronobiology, however, has thus far escaped the attention of entrepreneurs and historians of pacing, as did contributions on this topic with Earl or his staff as senior authors (12, 14; cf. also 15). But toward the goal of a chronobiologic timely pacer, the new science accumulates a set of maps in time, chronomes. These include maps of changes with an about 11-year near-periodicity (the circadecennian) of heart rate and heart rate variability (131, 135, 136), with a period corresponding to that of the Schwabe cycle of sunspots (88, 89). There are also biological near-matches of the about 21-year bipolarity cycle, described on the sun by Hale (137, 138).

*The future should be now.* On the theoretical side, the mapping of chronomes, chronomics, led to inquiries into our origins and our future in a budding chronoastrobiology (32, 33). As Earl often notes, these endeavors are not in the mainstream. The application of some of them seems urgent to one editor who spontaneously made these comments (19):

*Talking about "blood pressure" as a single figure is similar to knowing the average height of a mountain range: an interesting statistic, but completely useless to a pilot trying to make it through a mountain pass alive. Realistically, we need to consider not merely the mean [average] stress on an aging vascular endothelial cell, but the "peaks" that it has to "fly over" as well. Aging vessels are—to an extent—the end result of such stresses. Halberg et al. suggest that many patients may be apparently normotensive [with normal blood pressure], yet (because of circadian peaks in blood pressure) have the catastrophic risks of any other severely hypertensive patient. They recommend that [medical practitioners] avoid "flying blind" and begin to measure peak pressures more accurately if we are to avoid disaster.*

Another editor published a recent review of the status quo under the section title "Future history" (118). The senior author once received an invitation for a lecture, suggesting the



title “Medicine in 100 years” rather than “Prescription for the present”. In 1984, a publisher (without consulting the authors) put out a pertinent issue of his journal under the title “Chronobiology of blood pressure in 1985”, implying that chronobiologic blood pressure monitoring would be accepted within a year (139). At the time, the authors thought he was pessimistic, that chronomics were then to be implemented. In retrospect, he was too optimistic. A decade earlier, in 1974, Frederic C. Bartter, then head of the Hypertension-Endocrine Branch of the U.S. National Institutes of Health (NIH) and later director of the NIH Clinical Center, was convinced (140): He had a patient whose blood pressure had been diagnosed differently by two physicians who habitually saw him at different times of day. One, whom he saw in the morning, consistently deemed the patient normotensive; the other, whom he saw in the afternoon, diagnosed him as hypertensive. Bartter then hospitalized him for several weeks at NIH for study. Based on measurements around the clock for weeks in this case, he wrote:

*By conventional standards, this patient is clearly normotensive every morning. But the blood pressure determined each day at 6 in the afternoon provides especially convincing evidence that this patient is a hypertensive. ...*

*My plea today is that information contained in [data curves compiled under differing circumstances, such as 24 hours a day/7 days a week] become a routine minimal amount of information accepted for the description of a patient’s blood pressure. The analysis of this information by cosinor should become a routine. It is essential that enough information be collected to allow objective characterization of a periodic phenomenon, to wit, an estimate of  $M$  [MESOR, a rhythm-adjusted mean], an estimate of  $A$  [circadian amplitude] itself, and finally an estimate of acrophase,  $\phi$ . In this way, a patient can be compared with himself at another time, or under another treatment, and the patient can be compared with a normal or with another patient.*

The status quo of hurdles, and halting steps in which as yet only a very few of these were overcome, has been summarized in this journal (141). Among the hurdles still preventing entry into practice is the lack of generally available unobtrusive instrumentation for recording everyday physiology so that earliest alterations in time structure associated with an elevated risk of disease are detected and lead to prompt action.

**Marker rhythms.** Half a century ago, Earl Bakken built a device to record the motor activity of rodents. It served to obtain numerical data that allowed the assessment of several dynamic characteristics of a time series. A case in point was the assessment of the period and phase of each component in a spectrum of rhythms with a multitude of frequencies; it was also the quantification, with their uncertainties, of the double amplitudes and those of the harmonics of principal components. These were measures of the extent of predictable change as well as of the waveform. By 1950, Earl, then the young engineer, had lent a helping hand to what, thanks to him, was to become a Chronobiology Center at the University of Minnesota. His device helped abolish the slavery of nearly exclusive dependence upon data inspection by the naked eye. At the time, many scientists used these recorders to obtain

**Fig. 10. Earl Bakken: photo gallery.**

Montage of episodes from “One Man’s Full Life”.  
**a.** Photomontage depicting (from top to bottom) C. Walton Lillehei, Minnesotan pioneer in cardiac surgery, with a young patient for whom Earl provided an updated version of Medtronic’s first wearable, battery-powered, transistorized cardiac pacemaker, hailed as a “miracle” that kept sick kids alive, as originally published in *The Saturday Evening Post* in the late 1950s. By 1959, Medtronic’s family, while still small, had become a bit more “corporate” in appearance. Earl Bakken in sports jacket on far left; co-founder Palmer Hermundslie in suit and tie on far right. A big, bulky AC pacemaker was state-of-the-art technology during the early 1950s. While it was effective, especially in emergency rooms, its range was limited by the length of its tether to the nearest electrical outlet. After four weeks of work in

late 1957, Medtronic delivered the world’s first wearable, battery-powered, transistorized cardiac pacemaker to surgeons at the University of Minnesota. Within hours, the device was helping keep a pediatric heart patient alive. Dr. Samuel Hunter, who with Medtronic engineer Norman Roth developed a bipolar electrode that represented a major advance in pacing technology. First implanted in 1959, the Hunter-Roth lead helped contribute seven years of life to a local 72-year-old patient with Adams-Stokes disease. The Bakken Library & Museum in south Minneapolis, recognized worldwide as a one-of-a-kind center for the study of electricity in medicine and life. Medtronic’s first battery-powered pacemaker relied on circuitry borrowed from plans for an electronic metronome. A metronome was thus an appropriate prop for this 40th anniversary photo of Earl Bakken in 1989.

charts that showed times of motor activity of a laboratory animal in black, and times of rest in white. These behavior-day charts for time-macroscopy plotted activity as a thin line for each day, one day's record following below that of the preceding day, without any numerical gradation. Activity was usually not numerically quantified from the record as such. It made little difference whether the animal dashed or crawled. Behavior-day charts were also extensively used in the study of child development, notably to depict the alternation of sleep and wakefulness (21, 22).

It was cumbersome to extract numerical data from such charts. But murine activity onsets (or wakefulness in human infants) could be seen beautifully, notably when they drifted out of and back into synchronization with the societal day. These drifts could be interpreted as a sign that an individual had its own built-in, when phase-gliding, free-running periodicity; they led, depending on these records, to a nearly exclusively time-macroscopic field, relying primarily on an inspected, rather than computed phase, to estimate the period. A major feature of rhythms, namely their amplitude, was usually ignored. By providing a numerical record amenable to analysis, e.g., to assess the extent of predictable change within a day, by 1950 Earl liberated the Minnesotans from exclusive reliance on eyeballing. The latter is invaluable as a complement, but can never substitute for separating chaos and trends from predictable intermodulating spectral components. Chronomes cannot be mapped by most useful data inspection alone. Sadly, for this endeavor in basic science leading to marker rhythmometry and quantified free-running, he did not receive an also well-deserved prize, as he did for the pacemaker (134).

**Conditioned reflexes or free-running?** In the latest 1940s and earliest 1950s, rhythms were regarded as impressed from without; they were seemingly inextricably associated with the timings of meals, motor and other activity, emotions, and any other "stresses" (or rather strains) of everyday life. That they were built into us seemed remote to most others, who had not seen the inbred strain-dependent dynamics of certain blood cells (87; cf. 16). We discussed similarities with Earl, in terms of an ever-present rhythm, and noted differences among the rhythms in various genetically pure strains; the data prompted him to refer to a "free-running oscillator". We then used this concept as a model for building our "home", i.e., as scaffolding for the science of chronobiology. To continue the analogy, we refrained from using the scaffolding (oscillators) as a habitation (into which we move). We did not rename the dynamics of a cell or an organ or of the entire organism into those of an oscillator or clock. We proceeded instead to map the pertinent morphology, biochemistry and physiology, and eventually the psychology, sociology, meteorology and the much broader physics involved, Figure 9 and Table 1.

**Temperature marker rhythmometry postponed.** One of us (FH), with Earl, submitted a proposal to NIH to build and test, in human applications, a recorder of temperature and activity rhythms. Our proposal was not funded. As we subsequently learned, a local referee had described FH as being in such demand that it seemed unlikely he would stay in Minnesota and complete the job! (Half a century later, FH remains at the same location.) Instead of this project, Earl had the opportunity to also help a well-known heart surgeon, Figure 10. In so doing, he developed for long-term use the transistorized implantable cardiac pacemaker. Thereafter, he added devices and concepts to this feat, until he gradually attained the

nificant contributions to the company's technology. Bakken at Medtronic's 25th anniversary celebration in 1974, holding an oversized depiction of the Medtronic medalion, which as a silver-dollar-sized replica has been presented to every one of Medtronic's 20,000-plus employees the world over.

The North Hawaii Community Hospital, which opened in the spring of 1996, a patient-centered facility where the most advanced diagnostic and therapeutic technology is integrated with millennia-old healing techniques to bring "harmony to the health of body, mind, and spirit".

**Fig. 10. Earl Bakken: photo gallery.**

Montage of episodes from "One Man's Full Life". **b.** Photomontage depicting (from top to bottom): Earl Bakken in the president's suite (a 3-stall garage) at Medtronic's "world headquarters", c. 1950. A flannel shirt and jeans was the uniform of the day, everyday, during Medtronic's formative years. Bakken in 1986 with a 5-year-old patient who received a Medtronic pacemaker at the age of one month. According to Earl, the patient, now in her teens, is leading a healthy and happy life. The Bakken Society in August 1998: established in 1979, it honors Medtronic scientists and engineers who have made especially sig-



stature he enjoys now, as modestly but factually described by himself and others (11, 127, 128). The data documenting free-running, Figure 11, at the outset for about a decade, had to be obtained manually, with a thermistor and Wheatstone-bridge circuit. The telemetry of core temperature was developed subsequently with NASA's help in preparation for a Biosatellite study of rhythms (132). An original quantitative demonstration of the details of free-running and analysis with periodogram analyses, Figure 11, and of the merits of tumor temperature-guided chronotherapy, Figure 12 (113), both rested on manual measurements.

**Susceptibility-resistance cycles.** The demonstration of different effects of the same dose of the same physical, bacteriological or pharmacological agent and thus scientific chronotherapy, however, is based on laboratory investigation (106–117). In the 1950s, it was a surprise to learn that timing could contribute to the difference between life and death. Most or all mice of an audio-sensitive inbred strain could survive the ringing of a bell at certain times but not at other predictable times (106, 107). More generally, most rodents survived a fixed dose of a drug like ouabain or ethanol, at one clock-hour but not at another (108). The time of highest resistance was built-in, free-running in animals kept in continuous darkness (142; cf. 143, 144). The demonstration of a circadian rhythm in therapeutic index followed in the laboratory (113) and thereafter the implications were documented in the clinic, Figure 12.

The use of the marker chronomes of blood pressure and heart rate has started the timed treatment of overt blood pressure disorders; it has also served to detect and treat disease risk syndromes. Characteristics of marker chronomes, with chaos and rhythms, in a broader context, include trends. A gradual rise in the case of blood pressure with age has to be separated from pressure-related disease risk elevation. Chronome mapping can then be used for deciding in the light of chronobiologic reference values on whether to treat along the scale of age and, if so, when to treat, e.g., in relation to a circadian acrophase. The chronome of blood pressure may also serve for assessing the treatment effect, Figure 13. The

technology for unobtrusive monitoring and as-one-goes analyses with repeated passes over the accumulating data, which became the state of the science (no longer art) for the rodent, awaits transfer to humans for detecting lasting risks, excluding those tied to transient emotions and uncovering those brought about by drugs. Earl is the time-witness of these developments, and did what he could to support the science in the face of skeptical local administrators, in the only way understood by the latter.

**High touch added to high tech.** After placing “machines in our hearts”, Earl Bakken eventually broadened his interests, adding “high touch” to his endeavors in health care, far beyond mechanically restoring the rhythm to the heart, and restoring health with other devices for use by those afflicted with overt diseases. Herein, we honor Earl for his steady advocacy and support of chronobiology's major aims of detecting the subtle early risk-associated alterations that have to be uncovered for preventing disease. Whether by non-drug treatment and/or by drugs, we dubbed these endeavors “prehabilitation”, Figure 14 (131). The “p” in “prehabilitation” seeks to ring a bell by aligning it with rehabilitation, but with the important distinction pointing to its major advantage, i.e., that prehabilitation is implemented before the *fait accompli* of disease. An assessment of variability is required for the recognition of a disease risk syndrome. This is the practical benefit to be derived from splitting the normal range of variation into chaos, trends and rhythms, three of the elements of chronomes.

**Local hurdles.** Years ago, Earl and some of us traveled to attend conferences and see friends around the world. In China, Italy, Monaco, Norway and Spain, we sought to implement chronobiology's aims. Everywhere he was received with open arms and great respect. A hurdle to implementing chronobiology, however, emerged in Minneapolis, Minnesota. Earl kindly accompanied one of us to a meeting of the blood pressure committee of Group Health (now HealthPartners), a health maintenance organization. Early in the morning, perhaps before 7 am, we met with committee members who were motivated to get up well before office hours and were thus unquestionably

**Fig. 11** (next page). The components of the chronome are internally coordinated through feedsiderwards, in a network of spontaneous, reactive and modulatory rhythms. The endogeneity of a chronome component was first demonstrated, statistically validated and quantified by objective numerical measures of the uncertainty of its characteristics for the case of circadians in the blinded mouse models (I). In studies on the effect of the lighting regimen as a synchronizer, the question as to the transducer arose. Do the eyes mediate the effect? To answer this question, two models were studied: the blinded C mouse and the mouse born anophthalmic. In the study on blinded mice, the controls were sham-operated and had consistently on the average high blood eosinophil counts in the middle of the daily light span and low counts during the dark span. By contrast, the blinded mice showed the same result in one study and the opposite effect a few weeks later. It was postulated that the rhythm of the blinded mice may have a circadian period slightly different from that of the 24-hour synchronized control mice. Since it was not practical to bleed a mouse every 4 hours over a long span, rectal temperature was measured around the clock, in some studies for the lifetime of the groups of mice investigated. This work led to the discovery of free-running rhythms with a period that differed invariably from 24 hours, and also differed among some of the mice. It can be seen from the average rectal temperature curves of two groups of mice (IA) that the daily peaks occurred, on the average, about every 24 hours in the sham-operated mice. In the blinded mice, these daily

temperature peaks occurred earlier and earlier each day. Accordingly, a plot of the circadian acrophases as a function of time post-operation (IB) shows a downward drift to earlier and earlier clock-hours for the blinded mice but not for the control mice. A histogram of the estimated circadian periods (IC) shows that the sham-operated animals have a 24-hour synchronized circadian rhythm (the periods cluster very tightly around 24 hours; light bars), whereas the mice that had a bilateral optic enucleation have a circadian period shorter than 24 hours (dark bars). A deviant circadian period notwithstanding (the free-running circadian period of inbred C mice being shorter and that of a woman isolated from society longer than 24 hours), the internal timing can be preserved (as shown for three variables in ID). These experiments on mice establish, on an inferential statistical basis, the phenomenon of free-running of several variables of a circadian system with some degree of maintained internal synchronization after removal of the eyes (transducers for the primary environmental synchronizer, the 12-hourly alternation of light and darkness). Similar studies of the free-running of human as well as murine and other systems with circadian and also with other frequencies constituted an indirect demonstration of the endogeneity (i.e., of the genetic basis) of the chronome, now amply validated by chemical mutagenesis and gene transfer as well as by studies on twins. Rhythms being a fundamental feature of life, found at all levels of organization, it is important to recognize their coordinating role. Apart from the spontaneous

rhythms characterizing functions such as serum corticosterone or melatonin (IIA and B), reactive rhythms are found in response to a given stimulus applied under standardized controlled conditions of the laboratory: the adrenal response to ACTH is a case in point (broken line in IIA). Such response rhythms have been named  $\beta$ -rhythms, the spontaneous rhythms being called  $\alpha$ -rhythms, whether or not they are 24-hour or otherwise synchronized.

Much controversy can be resolved by studying the effect of the interaction by more than two variables at different rhythm stages; a third entity may modulate, in a predictable insofar as rhythmic fashion, the effect of one entity upon the second. Predictable sequences of attenuation, no-effect and amplification can then be found. A case in point is corticosterone production by bisected adrenals stimulated by ACTH 1-17 in the presence vs. absence of pineal homogenate (IIC). Such chronomodulation is also observed for the effect of ACTH 1-17 upon the metaphyseal bone DNA labelling in the rat (IID). Some of these multiple entity interactions involve more than one frequency; this is the case for the effect of the immunostimulator cefodizime (HR221) on corticosterone production by the adrenals stimulated by ACTH 1-17 (IIE). Chronomodulations involving one or several frequencies are known as  $\gamma$ - or  $\delta$ -rhythms, respectively; they are part of feedsiderwards, i.e., rhythmic sequences of attenuation, amplification and no-effect by a modulator upon the interaction of an actor and a reactor (III). © Halberg.

**ENDOGENOUS TIME STRUCTURE (CHRONOME) OF INTERNALLY COORDINATED FREE-RUNNING RHYTHMS (TOP)  
 THROUGH FEEDSIDEWARDS IN NETWORK OF SPONTANEOUS ( $\alpha$ ), REACTIVE ( $\beta$ ) AND MODULATORY ( $\gamma, \delta$ ) RHYTHMS (BOTTOM)**

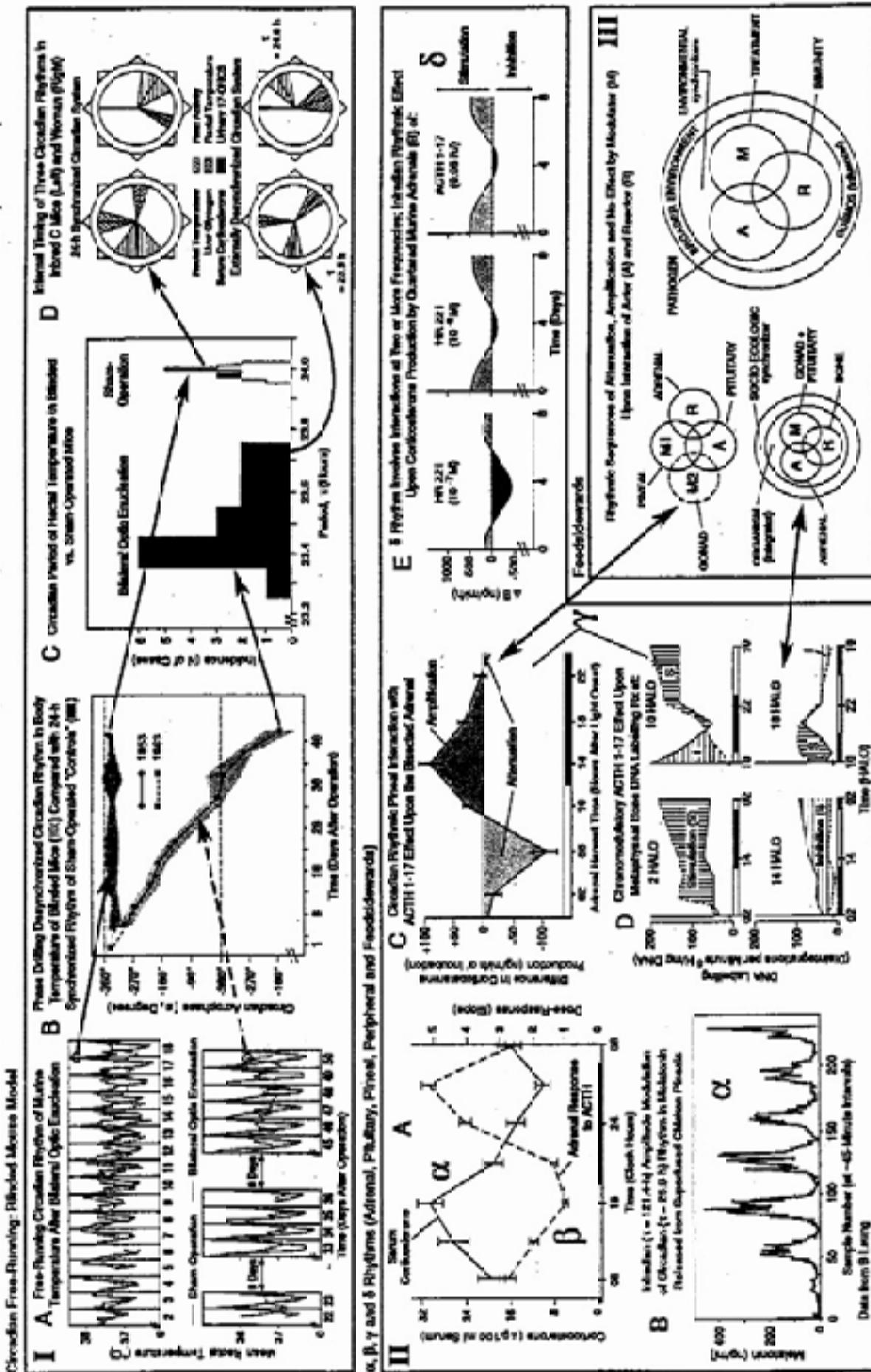
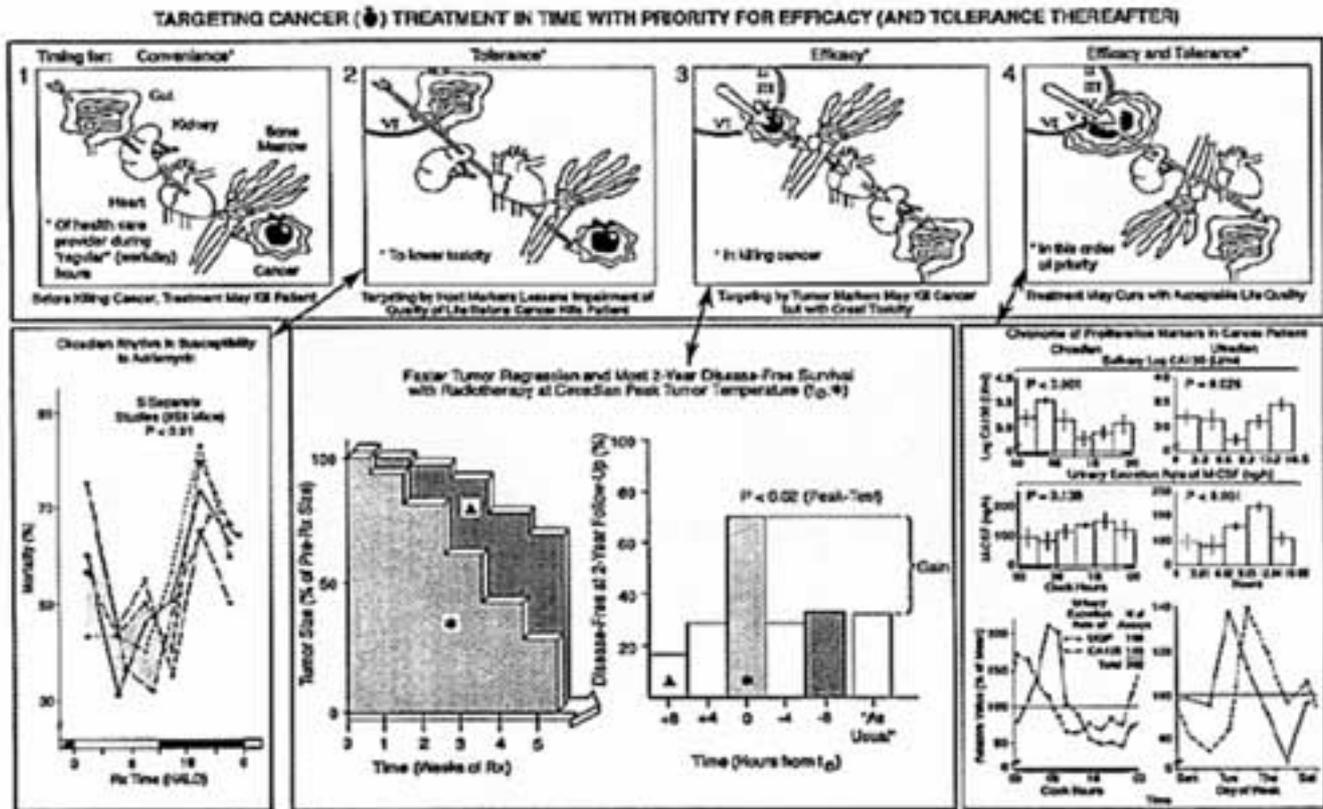


Fig. 11

sincere and well meaning. Judging from their questions, at least some of them may not have had the opportunity to meet Earl earlier. Those who conversed with us apparently did not know that, by then, Earl had been largely responsible for the creation of Minnesota Medical Alley (the statewide association of medical device manufacturers). Nor did they know, perhaps in view of his invariable modesty, that, as noted, his high-tech company had itself spread worldwide; certainly they knew neither about his introducing the concept of free-running in a new Minnesotan science, chronobiology, nor having built the pacemaker. Had they known all of this, they probably still

would not have understood his personal interest in health care as a whole. Earl the scientist and humanitarian pursued this interest with the same devotion as that with which he built Medtronic (11).

Since he was quiet, a committee member asked Earl "What do you do for a living?" Earl said, "Oh, I work for Medtronic". (Note that he didn't say he was the *founder* or the *chairman of the board* of Medtronic! Nor, what is most important for the history of chronobiology, that he was a prominent proponent of partly built-in aspects of circadian systems, Figure 11).<sup>5</sup>



**Fig. 12.** The treatment of cancer is usually scheduled by the convenience of the health care system first, according to the availability of the clinical facilities and of the physician or nurse. Chemotherapy being usually highly toxic, the drug may cause harm to various organs, from the gut and kidney to the heart and/or bone marrow. The cancer (shown as a crab) may also be hit, but the treatment by convenience may not be optimally planned. As a consequence, before killing the cancer, the treatment may kill the patient (I, #1). Acrophase charts are helpful for determining when a given agent is less toxic to the host; they make it possible to time treatment to minimize the undesired toxic effects of the treatment. This targeting for the times of the optimal tolerances constitutes an important improvement, but in itself it is not a sufficient advance. If the scheduling of the treatment takes into consideration only toxicity to the host, treatment may not be optimal in terms of killing the cancer. As a result, targeting by host markers lessens the impairment of life quality by debilitating and nauseating drugs, but it does not necessarily increase the treatment's efficacy (I, #2). The possibility of minimizing toxicity by timing is illustrated for the case of adriamycin (II). Results from five separate studies involving a total of 858 mice show that mortality reaches 80% when adriamycin is administered in the middle of the daily dark (active) span, whereas it is only 30% when given in the daily light (rest) span. Overall, the time when this drug is least tolerated is late during the dark (active) span. Translating these

results to humans, some usual clinic hours may correspond to a time when the host is most susceptible to the toxicity of this drug. It seems reasonable to seek the time of best tolerance for treatment as well as the best time for killing the cancer and to determine the best compromise: triangulation for chronotherapy. Large-amplitude circadian (and other) rhythms have been mapped for some tumor markers in saliva and urine, where they may not or at best only indirectly reflect tumor burden. The non-invasive assessability in serial samples of urinary or salivary rhythms, and any immediate decrease as an index of the time of drug activity could render these markers suitable for guiding treatment timing so as to optimize efficacy. Marker rhythm-guided chronotherapy was carried out with prednisolone on the LOU rat bearing a transplanted immunocytoma: the excretion of light chains by this tumor is circadian periodic for a large part of the lifespan remaining after tumor inoculation. In this very attractive model, a therapeutic gain of about 70% is associated with optimal timing in relation to the circadian rhythm in urinary light chains excretion used as a tumor marker (III, left). In the clinic, a relatively unspecific marker, namely cancer temperature, served for guiding the radiotherapy of patients with large tumors of the oral cavity (III, middle, right and bottom left). Radiation was applied for five weeks. Patients were randomly assigned to receive daily treatment at one of five circadian stages, either at the time of their daily peak tumor temperature (shown by a star) or 4 or 8

hours before or after that time. Peak tumor temperature was determined by assessing the circadian variation from repeated measurements of the tumor temperature, taken several times a day for a few days prior to the start of treatment. Tumor regression rate was largest for those patients receiving the treatment at the time of their peak tumor temperature. Patients treated at that time also had the largest percentage of disease-free survival at a two-year follow-up. Both in the experimental laboratory and in the clinic, chronotherapy is feasible and accompanied by large therapeutic gains. While targeting treatment in time by tumor markers may increase the chances of killing the cancer, the treatment may still be accompanied by great toxicity (I, #3). The longitudinal assessment of proliferation markers in a patient (EH, 72 y) with a müllerian duct adenocarcinoma involving the ovary reveals circadian, infradian (notably circaseptan) and ultradian components, notably with periods of about 14 to 16.8 hours, as illustrated for the salivary concentration of CA130 and for the urinary excretion rate of macrophage-colony stimulating factor (M-CSF) (IV). When, apart from their circadians and infradians, some tumor markers exhibit ultradian variations, and thus more than one peak per day, the best time can be sought to administer the treatment to optimize its efficacy first while also, as a secondary consideration, attempting to optimally shield the host from the treatment's toxicity (I, #4.) © Halberg.

Committee member (evidently believing Earl to be a sales or marketing person): "What do you peddle?"

Earl: "I peddle chronobiology because I believe in it, but Medtronic has no instruments [i.e., blood pressure measuring devices] to sell".

**The fallacy of transferring procedures used on groups to individuals.** The committee as a whole decided to ignore our chronobiologic recommendations of monitoring blood pressure and heart rate before an office visit: "This is not what national clinical trials do; what is good enough as a procedure funded by hundreds of millions of U.S. \$ in government-sponsored research is good enough for us". The committee was unaware of the fallacy of transferring without qualification to the study of individuals, procedures used on very large groups. They were unaware of fallacies in transferring inferences, e.g., computed correlations, based on data from groups, to the individual. The "ecological correlation" or "ecological fallacy" is a case in point (145, 146). Giant studies on blood pressure and sodium intake ignore inter-individual variability and timing. The tacit assumption of a relative constancy, or homeostasis, when none exists, does not justify inferences based on one or a few measurements. The limitations of the latter are sometimes somewhat compensated only by the large numbers of measurements. When many people each contribute a single value, the number of measurements is substantially increased by dozens or hundreds, and often by thousands of participants. These large numbers of participants are lacking when the procedure of single measurements is applied to the individual.

By the same token, inferences based even on many, not only a few measurements on *many* people, must not reliably guide action without measurements on a given person concerned. A recent handout from the American Dietetic Association (147) illustrates a sweeping sodium hypothesis. There are responders, with a high blood pressure in association with a high sodium intake; there are non-responders; and there are reverse responders. These individuals' blood pressure rises with a lowered sodium intake; in them, sodium intake is required to lower the pressure (148, 149; cf. 150, 151).<sup>5</sup> Except for an emergency, the spotchecks of blood pressure used in very large clinical trials on very many subjects must not be used in clinical practice. Taking the blood pressure only on a few occasions does not assess variability. When the measurement is done only once, as is usual whenever the value appears to be acceptable, there is no variability estimate whatever. This is the lesson "Mr. High Tech's" (Earl's) presence at the committee meeting, and his presence in spirit in this laudatio, should convey to the reader. In addition to serial measurements, there is also a need for a chronobiologic interpretation. Otherwise a very great risk present in association with "good" values will be overlooked, Figure 13, a graph prepared to support our request for data on Earl himself.

**From electricity to magnetism.** Earl's interests and those of chronobiology have more convergences. His love for electric-

ity, and consequently for magnetism, has led him to create The Bakken: A Library and Museum of Electricity in Life. With similar current interests, chronobiology, with the help of modern monitors, uncovers the electrocardiographic basis of associations of magnetic storms with myocardial infarctions and strokes. We find further associations of lesser magnetic disturbance with the "grids" of the human heart assessed by the damping of circadian frequencies of heart rate variability in the 7-day ECG of 14 students of Andi Weydahl in the sub-arctic (152; cf. 131). Chronomics reveals, in what was a heretofore controversial, since multifactorial and homeostatic field, that there are cycles in susceptibility not only along the scale of 24 hours but also along those of 10 and about 50 years in myocardial infarctions and strokes, respectively (33). By considering cycles, chronobiology accounts for many controversies resulting from studies carried out in different circadian (16) or circadecennian (118) or circasemicentennian stages.

Associations of geomagnetics are also found with the grids of the brain, assessed by human behavior, including religious motivation (153, 154). For instance, worldwide associations are emerging between "motivation", in a very broad unspecific sense, and the cycles of solar activity. The cyclic signature of the about 10-year Schwabe cycle of sunspots was seen first in one index, the number of proselytists in Alaska (154). Another index of religious motivation is the number of hours spent in work for their church by Jehovah's Witnesses. It shows worldwide a near-match of the about 20-year bipolar (Hale) cycle in most of 103 countries around the world (153).

Gauss, Humboldt and Sabine started learning nearly two centuries ago from the mapping of geomagnetics at different latitudes. In their footsteps, we now find a latitude-dependence of religious motivation, used in the want of a better index as a gauge of spirituality (153, 154). These findings have led to many new questions about some origins and current mechanisms of spirituality, a topic dear to Earl Bakken and his Archaeus Project (11) concerned with how the grids and humors of the brain function, i.e., about neuroendocrinology par excellence.

**Cancer chronotherapy.** Nearly half a century ago, the built-in cell cycle was demonstrated and features of this cell cycle chronome were mapped. This prompted the first successful human cancer chronotherapy, Figure 12. Groups of patients with certain very advanced perioral tumors, so large as to impair speech and eating, were treated. Radiotherapy was given at the time of peak of tumor temperature to one group; four other groups were treated 4 or 8 hours before or after the peak; and the last group was treated as usual, without considering timing. (Such tumors are now treated and/or surgically removed at a much earlier stage and are no longer encountered in that size, and hence are only of historical interest for an historic finding.) In those perioral cancers, Dr. B.D. Gupta semi-quantitatively rated the shrinkage of the tumors, an effect ascertained as being of high statistical significance.

5. For instance, the experiments that led to the coining of "circadian" systems had been dismissed as trite. The laboratory at the University of Minnesota was then lost. The studies of the murine temperature rhythm, after bilateral optic enucleation, Figure 11, had to be carried out at a state hospital about 40 miles from the university campus. What Earl had dubbed "free-running", and one of us "circadian", a word currently found in the title or abstract of over 1,000 scientific publications/year, was shrugged off as "paranoia". The actual uses of "circadian" or of

the biological week and decade, and chronomes more generally, to many still seem far-fetched. Earl did not, and does not now, share the prevailing attitude of too many administrative officers who gauge scholarship by the amount of grant support, not realizing that the funds granted on the basis of a review by peers represent the status quo and that consequently any endeavor unsettling the status quo first meets rejection; the more rejection, the more revolutionary the work proposed is likely to be. Much that was

unorthodox in the past was rejected or ignored, whether it was genetics or chronobiology.

6. Doz. Ludwig Pöllman, an occupational physician, related the case of a worker who invariably kept a salt shaker handy, despite a policy that those doing heavy parcel lifting work with him should drink plenty of fluids and adhere to a low-sodium diet. This worker had ascertained that his self-measured pressure went up when he was deprived of sodium and that sodium intake reduced the pressure.

The results on these patients, obtained by treating in relation to a marker rhythm bear on the topic of Earl's first chronobiologic endeavor. In the perspective of several decades, they justify our joint proposal to NIH of developing a temperature recorder for ambulatory use. Further, the results are of prospective interest. Timing, guided by a marker rhythm, can improve outcome in a chronoradiotherapy based on chronomics. Individualized circadian maps, in this first oncologic clinical trial, doubled the 2-year disease-free survival rate (155). Figure 12 shows this historic finding on marker rhythm-founded actual practical cancer chronotherapy.

**More on the biological decade or double decade.** The chronoastrbiological side of non-photic, invisible environmental cycles is documented in a book dedicated to Earl (156). The biological week, half-year, decade and double decade are cycles shared by our natural physical environment and ourselves. The history of the photic day and year repeats itself. The societal week may be due to the physiological intuition of the founders of the monotheistic religions. The about 7-day period happens to correspond in length to the period of a weak, wobbly non-photic aspect of our geophysical environment. This about-weekly wave train "free runs" naturally from society. It does not lock fully into an also-present precise 7-day anthropogenic cycle, which may also be present and, as already noted, increases with time in relative prominence; it is a potential index of magnetic pollution, perhaps more specific than the average yearly geomagnetic indices that undergo long-period wave trains, due probably to solar activity with similar cyclicality. Today, the week is built into us, as recognized first by Earl's criterion of free-running of decades ago (68). Now, the heritability of the week is confirmed by studies on twins (124).

Biological near-matches of other long environmental cycles are being detected in many biological variables. Single lifespans are too short to test them reliably for endogenicity by the criterion of free-running. For the moment a tentative criterion of endogenicity derives from parameter tests or, more conservatively, from the non-overlap of 95% confidence intervals of the period estimates, when they differ, and from differences in phase when the periods happen to be the same. These criteria can be used for a set of natural physical environmental cycles vs. a biological cycle. Cases in point are circadecennians, circavigintunennians or circasemicecentennians in neonatal anthropometry on the one hand, and in Wolf numbers, solar wind or geomagnetic measures on the other hand.

**The good and bad of society.** The grids and/or the humors of our brains need not wait for big storms; they respond by motivational changes to subtle natural environmental factors, not only in religious proselytism (153, 154). There are also cycles in murder as near-matches of the about 50- and about 20-year cycles in solar activity. This finding, based on a century of data analyzed thus far, Figure 15, awaits scrutiny for longer spans and thus for the resolution of even longer periodicities. Differences in phase, with non-overlapping 95% confidence intervals of the solar cycles and near-matches in frequency of both religious motivation and crime, if confirmed, could perhaps point to different mechanisms underlying some aspects of criminality vs. spirituality in the human brain and/or the environment. The task on hand is to clarify this problem cost-effectively by the study of all available archival records and initiation of systematic physiological recordings on an appropriate worldwide scale. The latter has already served to reveal direct ECG-recorded magnetic disturbance effects on the "grids" of the heart, exerted directly or indirectly (131, 156).

**Fig.13.** Demonstration that the scheduling of sotalol (betapace 80 mg) as one rather than two tablets per day can avoid the diagnosis of CHAT (circadian hyper-amplitude-tension, a condition characterized by an excessive circadian blood pressure amplitude) while maintaining the 24-hour blood pressure average (MESOR) within acceptable limits. Patient is 82-year-old man with coronary artery disease and a history

of coronary artery bypass grafting. Parameter tests indicate that by comparison with two tablets per day (around 08:00 and 20:00), treatment with one tablet daily taken in the morning (around 08:00) is associated with a similar MESOR of both systolic and diastolic blood pressure, a higher MESOR of heart rate (61 vs. 56 beats/min), a reduced circadian amplitude of systolic blood pressure (10.0 vs. 21.5 mm Hg;

$P < 0.001$ ) and diastolic blood pressure (6.4 vs. 12.6 mm Hg;  $P = 0.003$ ). The 24-hour standard deviation of heart rate is also increased (from 9.7 to 12.1 beats/min). Three months later, treatment consisting of a single tablet taken upon awakening is still associated with a circadian blood pressure amplitude well within the acceptable range (not shown). © Halberg.

**PRE-HABILITATION PREFERABLY BEFORE AS WELL AS WITH REHABILITATION  
(FOR VASCULAR DISEASE PREVENTION AND MORE GENERALLY)**

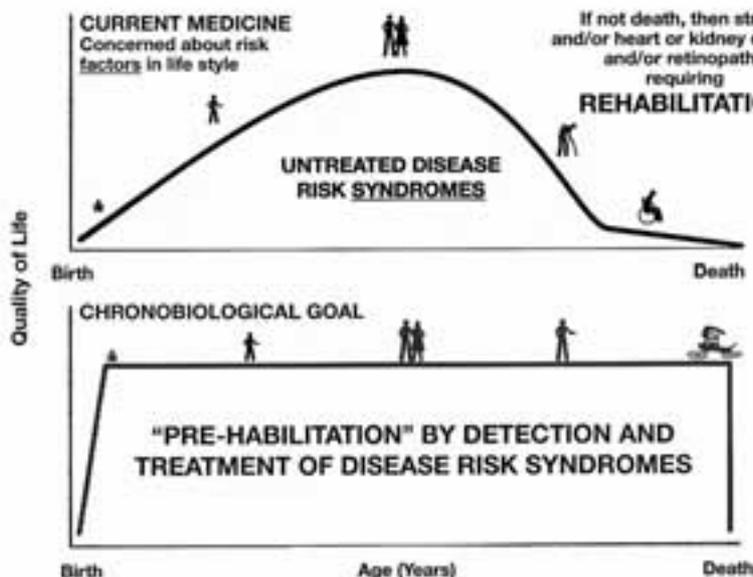


Fig. 14A

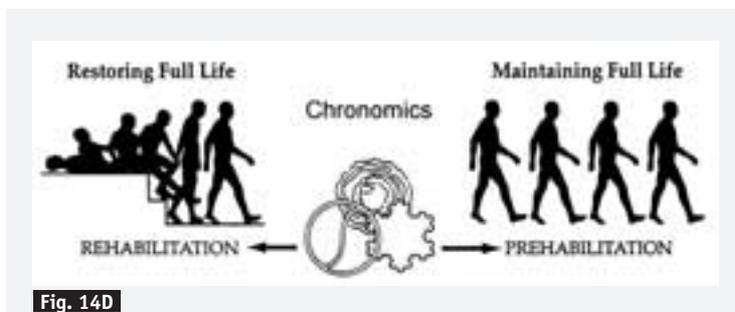


Fig. 14D

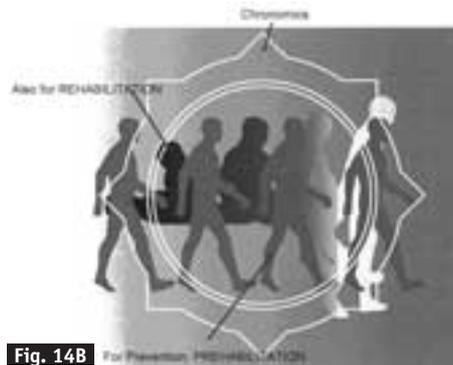


Fig. 14B

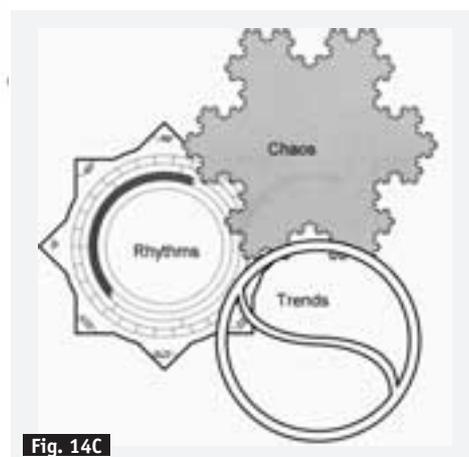


Fig. 14C

**Fig. 14. Pre-habilitation.**

**A.** Pre-habilitation, preferably before as well as after or with rehabilitation (for further vascular disease prevention and more generally). By the early detection of disease risk syndromes in the individual subject, countermeasures for primary prevention can be instituted. Such pre-habilitation in health can also complement rehabilitation in disease and can be a major goal of health care. Pre-habilitation would complement an across-the-board reduction of risk factors, the latter implemented by changes in lifestyle. For pre-habilitation, the development of preferably implanted instrumentation for blood pressure and heart rate monitoring and for automatic data interpretation is recommended. This can be achieved in the light of accumulating data bases (with outcomes already available for risk assessment) for the optimization (from the viewpoint of vascular disease) of what Earl Bakken described as health-related life quality.

Within such a framework, were it to account for all competing risks, the health-related quality of life would never be diminished until the very last moment when death comes and the organism collapses all at once. The primary concern is to maximize life quality by pre-habilitation, irrespective of whether such an endeavor should also help delay the collapse, i.e., maximize the lifespan (as it is likely to do). The health-related quality of life depends on a broader than vascular pre-habilitation. All disease risks must be lowered, so that those whose stroke is prevented do not suffer from cancer or other chronic diseases that also reduce life quality. Quality depends further on necessities for survival such as oxygen, shelter, food, water and freedom, which, with health, take precedence over ame-

nities related to physical, mental and emotional comfort. Mark Chatterton, a control engineer, has raised the question whether the necessities are multiplicative and the amenities (niceties, as he puts it) additive. For this overall maximization of life quality from birth to death, he thus suggests the integration of necessities, health included, with a summation of amenities. This line of thought could lead to a quantitative approach to overall life quality and quantity.

In the early 1980s, the late Otto H. Schmitt, another of Earl's friends, introduced the "Santosh Index", which he described as "a Sanskrit-derived expression for the individually perceived best possible 'Quality of Life' as a combination of components". This was intended "as an initial approach to a semi-quantitative algorithmic scale and dimensioned 'Quality of Life' measure, capable of being parameterized, studied for combinatorial interactive features and given an epidemiological data base". Otto's initial seed sprouted into several quite diversified ideas that are ripe to gain momentum from ongoing chronobiological womb-to-tomb mapping endeavors. Implementation and chronomedical improvement can include (paraphrasing Otto):

1. Whole Life Strand Chronoepidemiology, womb-to-tomb, ongoing in BIOCOS;
2. the development of an inexpensive, updatable, personally portable Whole Life Medical History and, from monitoring, a chronome card for vital signs. This card could be inserted into
3. a device for ongoing vital sign analysis (to provide an always-updated record of the patient's current state of health complementing and continuously updating this "status praesens" while also adding it to the online history);

4. paraphrasing Shakespeare, the past (history) then becomes (current state) prologue by the recycling of the data in repeated passes over longer and longer series to analyze, with any trends, rhythms with longer and longer periods;
5. an investigation of the collaterally hierarchical feed-side-ward-dependent access code structures of the consciously perceived quality of life and its time-dependent reprogrammability, complementing the self-rating of mental state and vigor;
6. the eventual co-optimization, by cost-benefit design levels of life quality for the individual, in the context of affinity groups, and the broader community and chronoeconomic Quality of Life; and thereby to strive for
7. health-related and broader, economic and political "happiness" studies (beyond polls) as a major new entry into the specialty of chronomedicine, and eventually
8. to arrive at a chronobioethic that focuses beyond transplants or, at the end of life, upon the quality of life at all ages, with investment into cost-effective preventive measures. © Halberg.

**B.** Chronomics provide the tools serving both pre- and re-habilitation.

**C.** The methodology of chronomics helps quantify elements of chronomes (multifrequency rhythms, chaos and trends) in us and around us.

**D.** Applications of chronomes extend focus to include, along with rehabilitation (left), pre-habilitation, that is the timely institution of prophylactic measures (right).

Appropriate analyses could well be the bridge between science and religion. They could lead toward the endeavor of optimizing pertinent chronomes in and around us. We may then aim at “returning to a full life” (Earl’s and Medtronic’s motto), not only patients with a failing heart, but also those with a failing brain and endeavor to strive in all cases for prehabilitation, Figure 14. Again, we must first find marker rhythms to detect earliest societal as well as individual risks in the neglected normal range. With this in mind, Earl’s Medical Alley may conceivably address the ills of society so that appropriate interventions may eventually succeed in emptying the nation’s prisons and fill the sites of spirituality.

**Urausu project aimed at safeguarding mobility and independence.** As to stroke, perhaps the most crippling disease, the program originally proposed in Roseville (141) is at the time of this writing administratively delayed there by a change in city management. Monitoring as a public service has been implemented as an official city-sponsored endeavor by Mayor Kaname Yamamoto of Urausu, on the island of Hokkaido, Japan, under the guidance of one of us (141). Data from dozens of 7-day around-the-clock monitorings of blood pressure and heart rate are available, with the main object of catastrophic disease prevention by risk detection and lowering, rather than waiting for the stroke or other incapacitating disease to occur. Somewhere, if not in Minnesota, a former Roseville mayor’s vision of mobility and independence throughout life is being actively pursued. Like Oliver Wendell Holmes’s “Deacon’s Masterpiece”, which Earl likes to invoke in his lectures, we try to secure for others a full life, without any attending ills. Chronobiologic preventive measures are being implemented by reliance upon monitoring and clarifying the problems of everyday physiology, including when to salt (150, 151; cf. 148, 149), when to eat (157) and when to treat, Figure 12 (155), or not to treat, Figure 13.

**Pacing health care.** Before the technology for placing machines in the heart began, sulfa drugs and penicillin changed the course of many infectious diseases. They keep many persons alive who a few years earlier would have died, as the elderly among us could witness in person. The pacemaker and the devices it spawned in turn keep innumerable people with heart disease alive, by restoring the most critical of rhythms, that of the heart. But Earl’s aims and actions in life are prompter and broader than those of Gerhard Domagk<sup>7</sup> and Alexander Fleming. Earl helped create the first timely and, in that sense, “*chrono*” therapy, involving cardiac pacing before the heart fails irreversibly. Eventually, the pacemaker will not

only restore a basic rhythm, but will do so chronobiologically, beyond adjustment to changes in daily activity. Pacemakers could anticipate, rather than merely respond to, the different chronome elements, including the consideration that a jittery heart is healthier than too regular a beat.<sup>8</sup> The story of the Activitrax pacer, from an entrepreneurial viewpoint, is told elsewhere (127; cf. 128). A truly chronobiologic anticipatory pacer is yet to be developed (12–15).

Whether the health survey now started in the residents of a Japanese town becomes a public service or is privatized is in the hands of government. The telemetry technology spawned by chronobiology is now extensively used for laboratory tests of drug effects. The electrical potentials of the very small mouse brain or heart are subject to as-one-goes monitoring. Earliest warnings for humans as well could thus be detected and could lead to consequent action by continuing to close the loop between diagnostic and preventive treatment devices, Figure 16 (131). These steps could assure the risk-free health of humans, if not (yet) the war-free life of societies, and the integrity of their environment for generations to come.

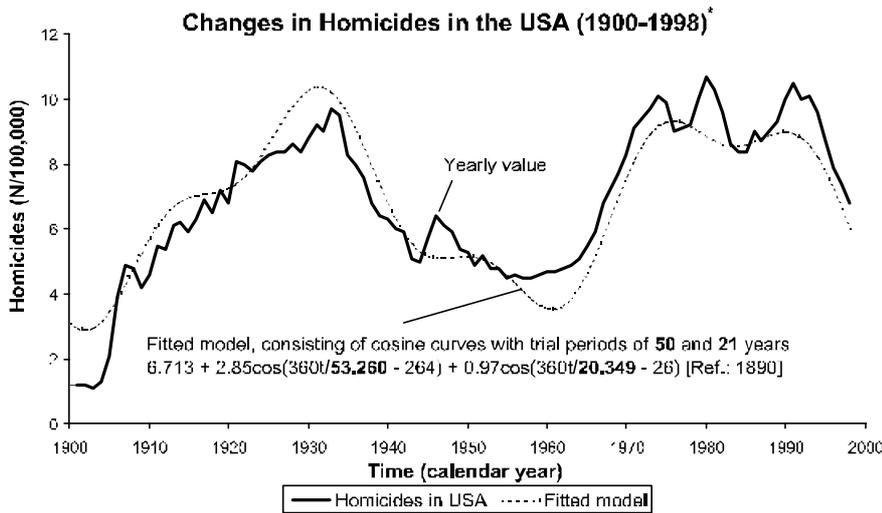
In Earl, chronobiology and now chronomics have had a mentor, a lifetime companion and indeed initially an active participant when it mattered most. Earl’s friendship with chronobiology started half a century ago, prior to his other concerns. Chronobiology assures his niche in the history of human endeavors, with, but also far beyond, the pacemaker in a much broader timely and timed preventive as well as curative health care. Some of his pursuits, which may appear to be utopia for those living today, can become reality for some future generation. In our lifetimes, this spells chronomics, the concomitant coordinated mapping of make-ups in time in ourselves and in our environment, near and far. Thus, we find invisible as well as visible, novel biological and environmental cycles, already reviewed in part earlier by Dewey (158), and matching physical and biological dynamics. Otherwise, brain, gene and protein research and the care provided in hospitals and offices will continue to build (like the blood pressure committee of Group Health or the putatively controlled clinical trialists of our day, and the vast majority of contemporary scientists and practitioners) on the quicksand of single samples in a dynamic, highly variable world.

Earl’s pivotal role is properly recognized in a scholarly book by a professorial specialist in the history of technology (127). This author concludes factually that many individuals contributed to the pacemaker and other high-tech health care devices, that really work, but he adds the sobering thought that they add billions to the nation’s medical bill. The under-

7. From Sutcliffe and Duin (74), p. 106: “In 1932, [Domagk] found that one azo [dye] compound—Prontosil red—cured mice injected with a lethal dose of haemolytic streptococci. Oddly enough, he did not publish his findings until February 1935. His employers later explained the delay by saying that Domagk had spent the intervening years confirming his results. However, when his report was finally issued, it consisted of only one animal experiment and a few sketchy case histories of human subjects. “Intrigued by Domagk’s report, scientists at the Pasteur Institute in Paris asked for samples of Prontosil for investigation; again there was a delay. In the meantime, the French team synthesized the drug themselves and verified Domagk’s results. However, they found that Prontosil would work only when the compound split into two parts within the body, and that

one of the two parts—later called sulphanilamide—was largely responsible for Prontosil’s bacteriostatic action (it did not kill bacteria like an antibiotic, but prevented them from multiplying). “Scientists were surprised that Domagk had made no mention of sulphanilamide, which was superior to Prontosil if only because it did not turn patients bright red. A British bacteriologist, Ronald Hare, came to the conclusion that Domagk had been aware of sulphanilamide but, for commercial reasons, had kept its existence secret. “Hare believed that Domagk and his associates knew that sulphanilamide was unpatentable because it had already been synthesized—by a Viennese student, Paul Gelmo, who had published his findings (concerning the chemical’s efficacy as a dye) in his doctoral dissertation in

1908. Therefore, surmised Hare, Domagk had spent the years between 1932 and 1935 in a vain attempt to find a drug similar to but better than sulphanilamide and one that could be patented. In the meantime, thousands of patients had suffered, and some had died—all for the sake of profits.”  
8. Beyond optimizing the pacemakers of today into anticipatory ones, we face the task of recognizing indications for them in the physiological range. This timely as well as timed implantation is a challenge to health care research and engineering alike. Worth testing are the putative merits of restoring an under-threshold variability in heart rate, which constitutes a very high risk of stroke, with as yet unproved etiopathogenetic roles.



\*National Center for Health Statistics (Homicide rates from the Vital Statistics: <http://www.ojp.usdoj.gov/bjs/glance/hrmt.htm>)

Fig. 15

Fig. 15. Cycles of about 50 and about 20 years are validated by linear-nonlinear rhythmometry for homicides in the USA (1900-1998), as evidenced by relatively tight 95% confidence intervals for the respective periods (53.26 y: 50.80-55.96; 20.35 y: 19.39-21.43) and by the non-overlap of zero of the 95% confidence intervals for the respective amplitudes (not shown). © Halberg.

Fig. 16. Closing the loop between diagnostic and therapeutic devices via chronobiology may lead to *chronomedicine*. The addition of a memory for data storage and for chronobiologic data analysis as-ongoes, according to the principles of (repeated passes for) windowing (i.e., analyses in spectral regions of progressively lower frequencies); compacting (in the form of the characteristics of the rhythm with the just-analyzed frequency); and recycling for the analyses on longer and longer series and the (preferably automatic) interpretation of the results, in the light of time-specified reference standards, could provide a bridge between monitoring endeavors aimed at screening, diagnosis and prognosis, and instrumentation for the delivery of treatment. In thus closing the diagnostic and therapeutic loops, a step could be made toward the online optimization of treatment by timely and timed treatment according to rhythms. © Halberg.

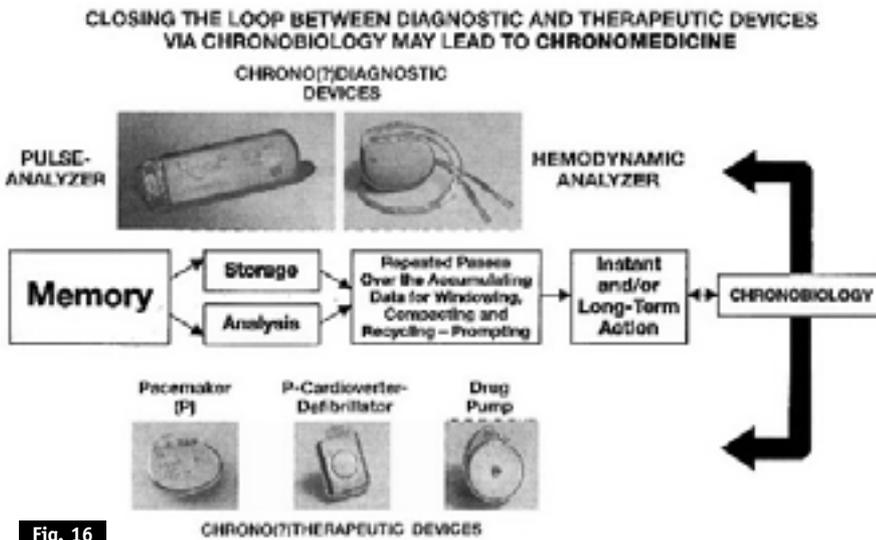


Fig. 16

Fig. 17. Challenge to engineers, to civil servants dispensing government resources, and to each individual interested in self-help. Investment into physiological monitoring and education in chronobiology, to detect warning signs indicative of an elevated risk, rather than only of the fait accompli of disease, can prompt preventive intervention with the goal of avoiding the crippling of catastrophic diseases, also a major drain of financial resources. By placing added emphasis on prevention, health care costs could decrease while the quality of care is improved. © Halberg.

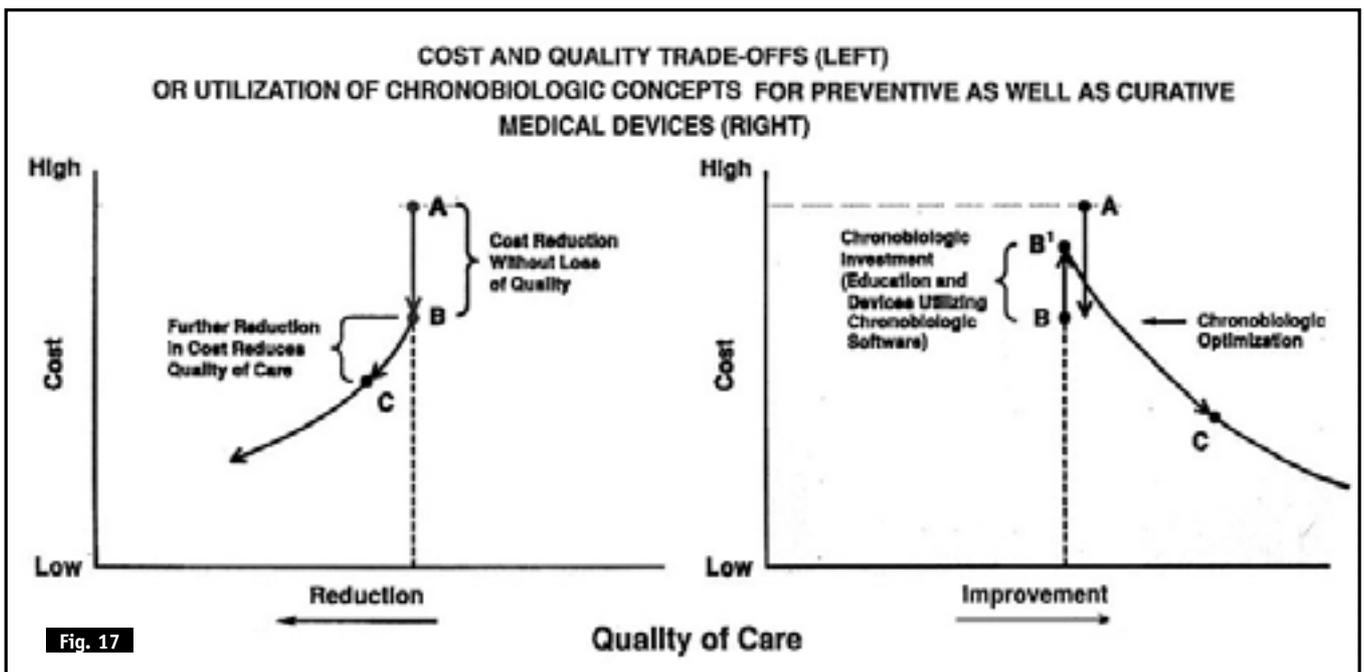


Fig. 17

signed, admittedly biased friends may be forgiven for predicting that the history of science and that of entrepreneurs are not necessarily related. When all is said and done, along with pacing the heart, Earl Bakken will also be remembered for his unrelenting contributions in all ways possible to a new science for prehabilitation, Figure 14, and thus for reducing cost while improving health, Figure 17. In an even broader perspective, free-running rhythms are built into our brains and hearts and into organisms and populations, into greater and greater wholes with longer and longer periods, including circavigintennians and circasemicentennians, even into religious motivation and criminality. Now, we must chart their course and analyze their mechanisms in order to deal with the ills, overtly demonstrated on September 11, 2001, in New York and Washington DC, of individuals and societies. In all these cases, Earl Bakken, the leader in the development of costly devices for rehabilitation, was also there during half a century to support marker rhythmometry, both for after-the-fact individual and eventually societal chronotherapy and for society-wide pre-habilitation.

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