The costs of ignoring a long-overdue chronomedicine: The chronome initiative emerging from the catacombs

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Abstract

OBJECTIVES. This position paper, revolving around the psychology of most health care providers, accompanies a case report in a companion paper in this issue. The topic is "the million-dollar baby", so named since the cost of his on-and-off hospital care for the first 13 months of his life was accounted to be U.S. $615,000, and his hospitalizations continued for another 13 months, presumably at a similar cost. Such an ordeal may be avoided if chronobiologic evidence would gain entry into the mainstream, e.g., by routine 7-day or, if need be, longer blood pressure monitoring with chronobiologic analyses. These activities belong in practice, rather than being relegated to research.

DESIGN. Historical parallel between the difficulties of introducing antiseptic and chronobiological principles, the latter focusing, in the face of an acceptable mean, on an altered variability, as illustrated in a case report and in follow-up validations on 297 and 424 patients.

RESULTS. Just as we now recognize the merits of scrubbing before surgery, the information contained in the dynamic characteristics of physiological variables such as blood pressure should be considered in medical practice, whether the variability occurs within or outside the usual value range. The systematic monitoring of vital signs in health serves to derive time-specified reference values for the interpretation of single measurements and of rhythm characteristics, thus refining the definition of health, rendering it positive and quantitative, thereby replacing the negative current definition of health as the abstence of disease.

CONCLUSION. Chronobiology should no longer be regarded as the study of confounding epiphenomena, but enter the mainstream of medicine by detecting and treating high vascular disease risk.

Dedication

The article was originally dedicated to the memory of the late Norberto Montalbetti, Professor and Head of the Department of Laboratories at Niguarda Hospital, Milan, Italy, and former President of the Section of Clinical Chemistry of the International Union of Pure and Applied Chemistry. He was an internationally active advocate of a human chronome (time structure) initiative, which he recognized as an endeavor required in its own right. He also visualized the complementarity of the endeavors mapping the human genome and those mapping chronomes. Chronomes characterize variables of both organisms and their environments near and far. Chronomes in dense and long data series consist of several elements. A spectral element of multifrequency rhythms is superimposed on deterministically or otherwise chaotic elements. Trends, the third element, characterize both endpoints of rhythms and chaos. In biology, chronomes rather than single sample snapshots on roller coasters are the phenotypical complement to the genome, adding to the latter a dynamic dimension of normalcy. Without the chronomic definition of health the genome initiative remains in its current homeostatic straitjacket, focusing mainly on the over 5,000 known genetic diseases. Prior to the coining of "chronomes" (Halberg et al., 1991; Cornélissen and Halberg, 1992), yet concerned with the mapping of the time structure, were several other outstanding late medical administrators, chronobiologists themselves, whom we wish to remember herein, all associates in research and friends:

- Frederic C. Bartter (of Bartter syndrome fame), Head of the Hypertension-Endocrine Branch and thereafter Clinical Director of the Clinical Center at the National Institutes of Health (NIH), Bethesda, Maryland, USA;
- Florian Delbarre, Professor of Medicine and President of the Université Rene Descartes in Paris, France;
- Howard Levine, Director of Medical Education at New Britain (Connecticut, USA) General Hospital and Professor of Medicine at the University of Connecticut in Farmington;
- Mortimer Lipsett, Director, National Institute for Child Health and Human Development, NIH;
- Jacques Mirouze, Professor and Head, Department of Medicine, and President, University of Montpellier, Montpellier, France;
- Kentaro Takagi, Head of the Department of Physiology, later Dean of Nagoya State University and a councilor in Japan's parliament, its Diet.

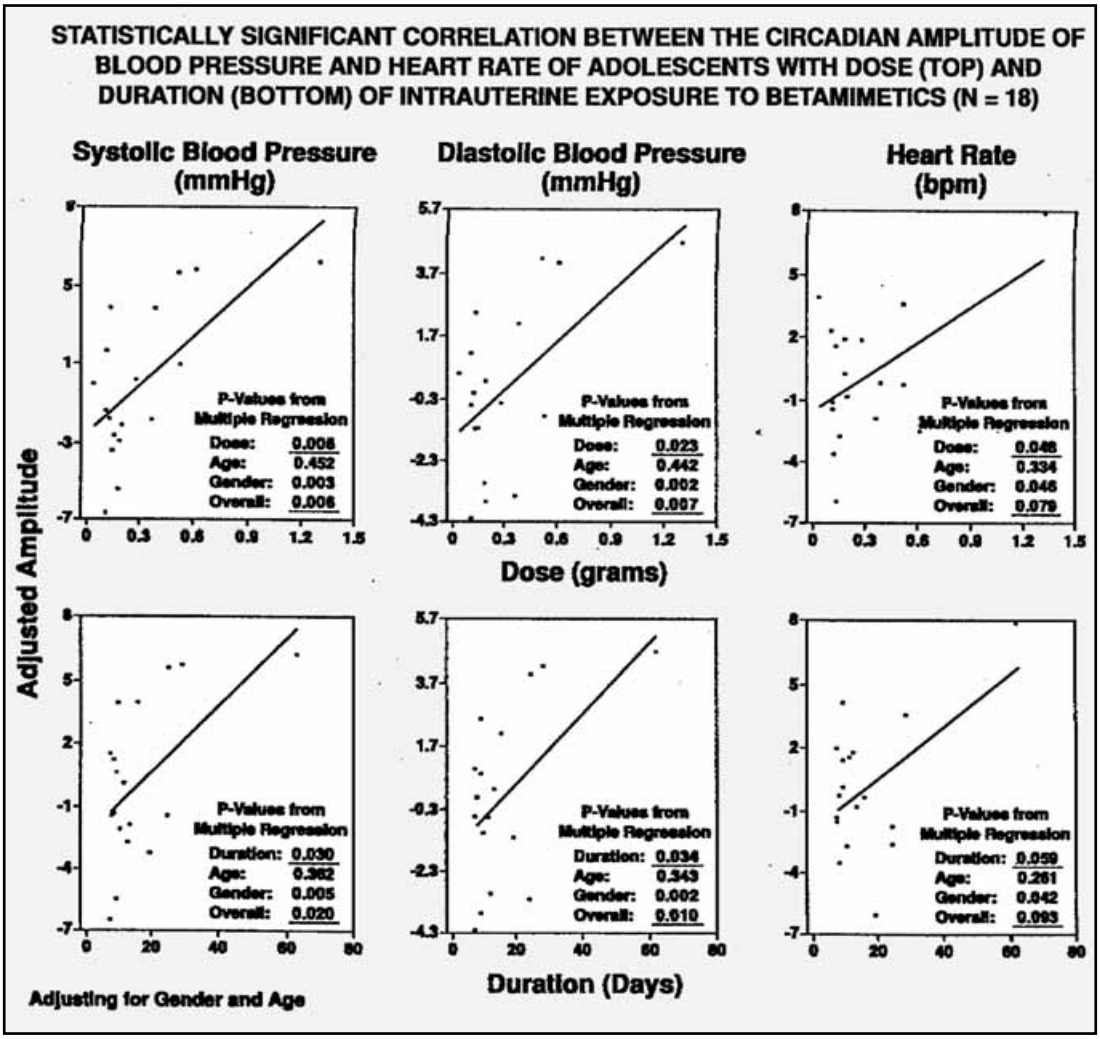

Figure 1. Intrauterine exposure to betamimetic drugs is associated with an increased circadian amplitude of blood pressure and heart rate in adolescence and with an increase in the left ventricular mass index (LVMI), the latter not shown (Syutkina et al., 1995). Both an excessive circadian blood pressure amplitude and an increased LVMI carry a large vascular disease risk. In view of these undesirable effects which last for over a decade, the use of betamimetics in pregnancy should be timed to seek a harmless window or omitted. © Halberg.

Among the living, enabling the start of a human chronome endeavor at the Chronobiology Laboratories of the University of Minnesota are:

- Earl Bakken, engineer father of high tech, to whom we owe the implantable cardiac pacemaker and the chronobiologists' concept of free running.
- Duane Alexander, pediatrician and current Director, National Institute for Child Health and Human Development, NIH; who with Claude Lenfant, Director of the National Heart, Lung, and Blood Institute, overrode referees in providing a substantial grant, enabling the work reported herein and in the case report.
- Dana Johnson, pediatrician, professor and head of neonatology at the University of Minnesota. With him, along with Joseph Rigatuso, Associate Clinical Professor of Pediatrics at the University of Minnesota and Director of Research at Health Partners Inc. (Minneapolis, Minnesota), we originally presented a case which typifies the suffering and cost associated with the benign neglect of chronobiology and thus describes the status quo.

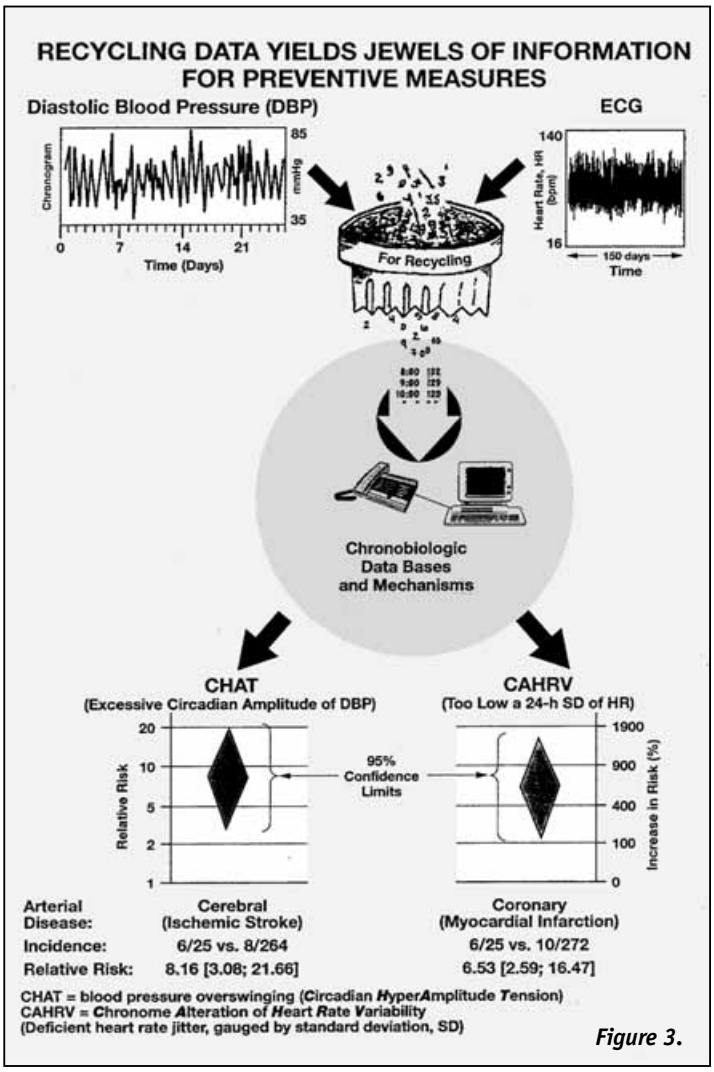

Figure 3.

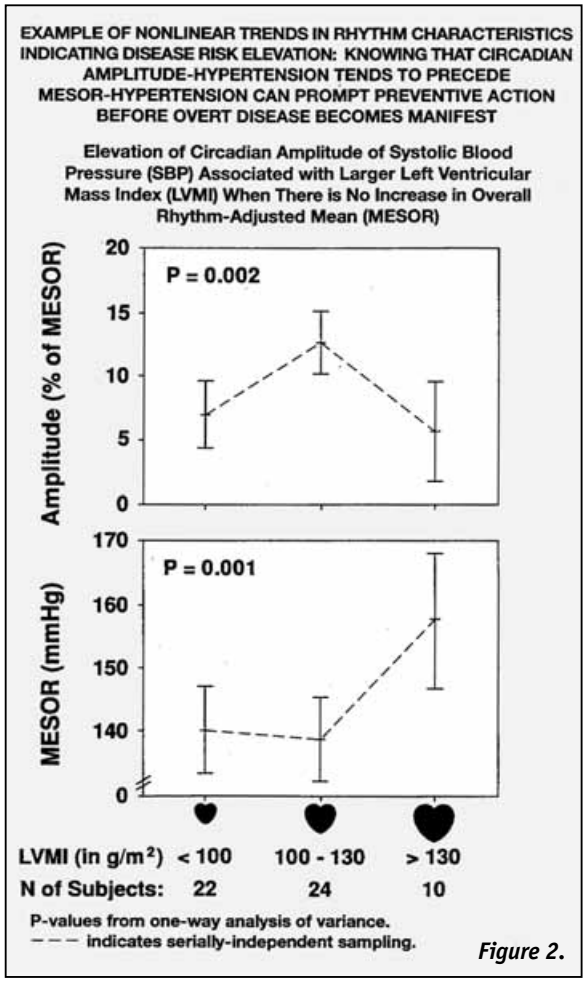

Figure 2.

Figure 2. Circadian blood pressure amplitude (top) or MESOR (bottom) show relation to the left ventricular mass index (LVMI). This finding of a (transient) elevation of the circadian blood pressure amplitude supports the proposition that MESOR-hypertension may be preceded by a transient circadian amplitude-elevation, the latter being an intermediate stage in the development of high blood pressure (Kumagai et al., 1992). © Halberg.

Figure 3. Risks (and uncertainties) associated with two disease risk syndromes (bottom), i.e, **c**ircadian **h**yper**a**mplitude**t**ension, CHAT (left), and, e.g., with a reduced heart rate variability, a CAHRV (right). These syndromes could be routinely diagnosed by chronobiologic computer analyses (middle) of time series accumulating in hospitals from recovering ambulatory patients and from intensive care units that are now trashed (top). © Halberg.

An analogy

Fred, Florian, Howard, Mort, Jacques and Kentaro, enamored of chronobiology yet seeing it remain a wallflower, outside the mainstream, might have felt as did Ignaz Semmelweis (1818-1865) as he completed his *magnum opus* on puerperal fever by writing: "If, God forbid, I should not reach the happy time when I can see with my own eyes, the acceptance of the prophylaxis of puerperal fever [read chronobiology in the context of stroke prevention chronobiolgy], I shall be enjoying in the hour of my death the conviction that sooner or later this time will unquestionably come." Semmelweis had earlier challenged his colleagues, who refused to scrub before surgery or before obstetrical examinations, with "The killing must stop ! In order to stop the killing, I shall keep watch, and anybody who will dare to perpetuate dangerous errors about puerperal fever will find in me an active opponent !"

The history of puerperal fever at the end of this millennium has several parallels in the status quo:

1) In the neglect of the fact that chronobiologic methods can help spot warning signs and thus help avoid preeclampsia (Cornélissen et al., this issue); that these methods recognize undesirable effects of the intrauterine exposure to betamimetics, Figure 1 (Halberg et al., 1990; Maggioni et al, this issue; Syutkina et al., 1995), that the procedures of the new science recognize circadian amplitude-elevation with an increase in the left ventricular mass prior to the occurrence of an elevation in the rhythm-adjusted mean of systolic or diastolic blood pressure, Figure 2 (Kumagai et al., 1992), and that an excessive circadian amplitude of diastolic blood pressure represents the great risk of ischemic cerebral events, while an insufficient variability of heart rate represents a high risk of myocardial infarction. These warnings, Figure 3, should prompt intervention for the prevention of heart attacks and stroke (Halberg et al., 1998);
2) In the need for the timing of anticancer treatment targeted by the use of marker rhythms (Halberg et al., 1977, 1992). This approach has already doubled human 2-year disease-free survival by the use of a marker rhythm for the radiotherapy of advanced tumors of the mouth and has achieved cures by the targeted timing of chemotherapy in experimental animals, where such cures could not be accomplished otherwise (Halberg et al., 1977, 1979). The approach is most promising with the recent discovery of five ovarian tumor marker chronomes that can guide clinical chronochemotherapy (Cornélissen and Halberg, 1994); and
3) In laboratory medicine more broadly, chronobiology provides the dynamic reference standards that split the normal range, whether we explore cardiovascular prophylaxis by aspirin (Cornélissen et al., 1991) or the risks of major diseases of our civilization: cardio-cerebro-reno-vascular conditions, breast or prostate cancer, emotional depression and a tendency to alcoholism, to mention only a few conditions (Halberg, 1983). Today's reductionist scientific climate can hardly afford to ignore that, as a function of timing, the same dose of the same molecule can inhibit or stimulate DNA synthesis (Walker et al., 1985). The difference between a stimulation and inhibition of a malignancy by the same total dose of an immunomodulator is also noteworthy (Halberg E. and Halberg F., 1980). The shift from main focus upon overt disease to disease risk syndromes is made possible by resolving otherwise unharnessed, confounding variability.

Footnote

1. Semmelweis spent the final years of his life in an insane asylum. The sanity of one of us (FH) was also questioned in relation to the very studies that led to his coining of "circadian" and eventually to the development of a new science. In Minnesota in the early 1950s, the average period of the rectal temperature rhythm of blinded as compared to that of sham-operated mice in an around-the-clock record covering a few days deviated very slightly from precisely 24 hours. He interpreted this deviation as an index of the rhythm's built-in nature, as a new dimension of our make-up in time, now the chronome. He also realized that we were at the threshold of resolving a terribly confusing source of variation. If one of two groups being compared free-runs and the other is 24-hour synchronized, it can be seen in consecutive comparisons that for a while a given group is higher and thereafter the same group is lower than a control group. These changes are unpredictable unless the free-run is recognized and the period assessed objectively by inferential statistical methods. Hence, he (FH) decided to scrutinize this finding further by continuing measurements around the clock for as many days or years (it proved to be years) as were necessary to establish the statistical significance and the degree of generality of the finding. That decision to keep on measuring, based on an extremely small difference, was originally labeled "paranoia" and caused the transient loss of his laboratory. The "paranoia" was amply validated thereafter by studies continued for further years on end by himself as well as many others.

Semmelweis' superiors discontinued his position. Prior administrators at the University of Minnesota never invested into a position for chronobiology and had nothing to discontinue. They accepted the support of the National Aeronautics and Space Administration (NASA), whose administrator, with his colleagues from the U.S. National Institutes of Health (NIH) and the U.S. National Science Foundation (NSF) brought about the Chronobiology Laboratories at the University of Minnesota that functioned as a *de facto* center for four decades. A few years before these laboratories' director (FH) reached retirement age, however, there was an attempt to block the continuance in support of chronobiologic activities of a lifetime career award from NIH (which NIH then spontaneously continued without any age limit). While in 1987 a report on "Focus" suggested that chronobiology space be reassigned to clerical accounting staff, some activity reflected in this seminar continues. Let us hope that the parallel with Semmelweis stops here.

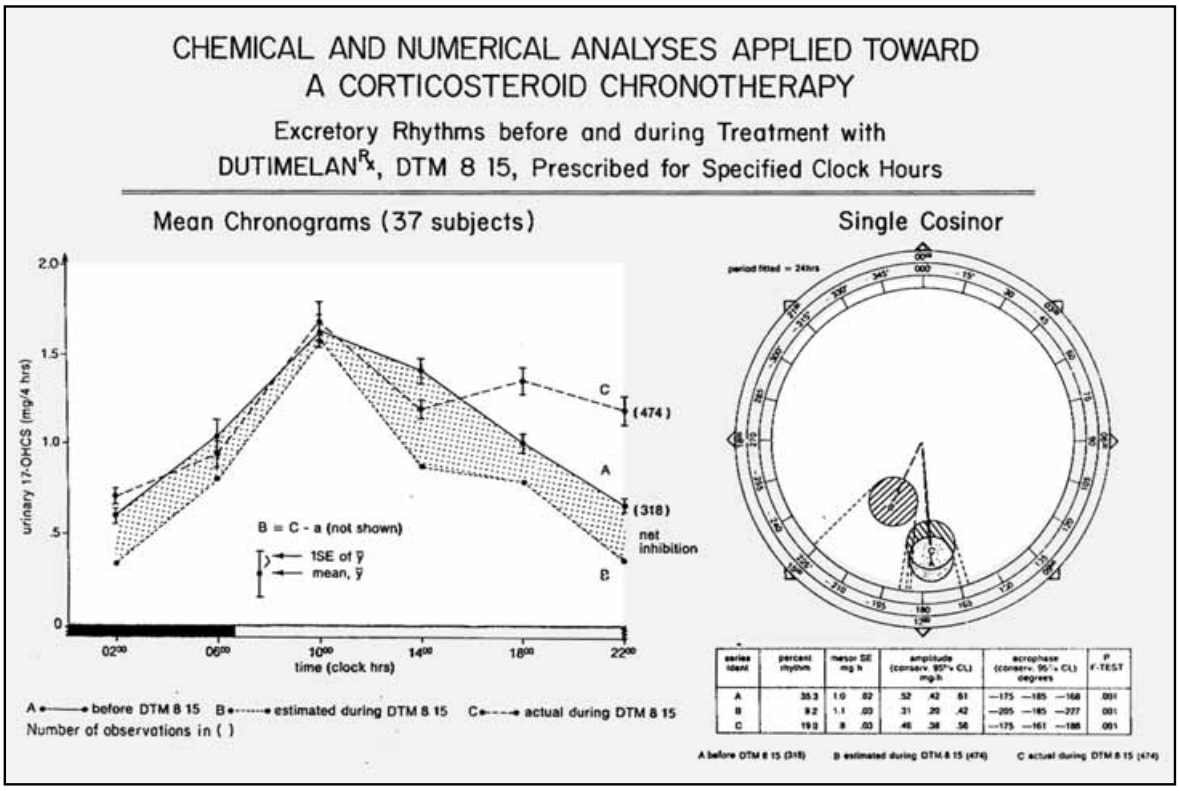

Figure 4. Chemical and numerical analyses applied toward a corticosterone chronotherapy. Excretory rhythms before and during treatment with Dutimelan®, DTM 8 15, prescribed for specified clock-hours (Carandente and Halberg, 1991). © Halberg.

We should know what time it is at all organization levels. With several journals fully devoted to it, chronobiology has emerged from the catacombs to occupy the interest of international conferences ranging from pathophysiology to neuroimmunomodulation and from physiology to clinical biostatistics. But even in dealing with variables such as blood pressure or circulating cortisol, chronobiology as yet has not entered the mainstream of medicine. It was a further good sign that a purely clinical journal, Il Policlinico, assigned a major section to chronobiology, but it did so only briefly. We will learn how to deal better with the *status quo* by turning again to a mid-19th century precedent, the resistance against antisepsis.

Historic scenario

By 1843, the contagious nature of "childbed fever" had already been recognized by Oliver Wendell Holmes (1809-1894), the noted American practitioner of medicine who was also both author and teacher. Semmelweis confirmed him four years later in Austria, yet a matter as cut-and-dried as antisepsis continued to be ignored by the medical establishment of that day. Conceivably, we not only count our blessings, but by pointing to history we may be able to persuade administrators that the time for the emancipation of chronobiology and its integration into the medical curriculum has arrived.

Before 1843, in Cordova, Spain, in the twelfth century CE, Averroës (1126-1198), the pantheistic Islamic scholar of law and philosophy, also learned in medicine, forced into hiding for a time on suspicion of heresy, apparently insisted on washing the hands before surgery. Other Arab physicians of Cordova followed the practice. When handwashing was transferred to surgery is unknown, but the merits of cleanliness as such had been recognized in priestly Jewish documents dating at least 500 and perhaps 1300 years before the Common Era (Exodus 30: 17-21) (personal communication by Leonard A. Schoolman). The washing of the hands before meals and before any ritual act may have eventually led to the requirement of cleanliness before surgery by the time of Averröes if not earlier. To some extent, the atmosphere eventually recognizing the need for scrubbing was prepared for thousands of years, even if the resolution of bacteria by the microscope was to give it a rational basis. Today, hygiene generally and scrubbing involve very many aspects of medicine.

All of this past history was ignored or forgotten when, in 1784, the Austrian Emperor Joseph II founded an obstetrical clinic at the General Hospital in Vienna: he wished to reduce the suffering of unwed mothers and to stop the many infanticides that took place at the time. The mothers-to-be were cared for by physicians who taught medical students, the best the health science of the day could offer. Nonetheless, by the third decade of the nineteenth century, this refuge for women and girls in trouble had become a place of death. One epidemic of puerperal fever followed another; pregnant women lying next to each other in rows were suddenly stricken one by one.

In 1834, a second clinic was founded exclusively for the training of midwives. It soon became evident that while in the physicians' clinic at least 10% and sometimes as many as 31% of the women died, the corresponding mortality rate at the midwives' clinic was

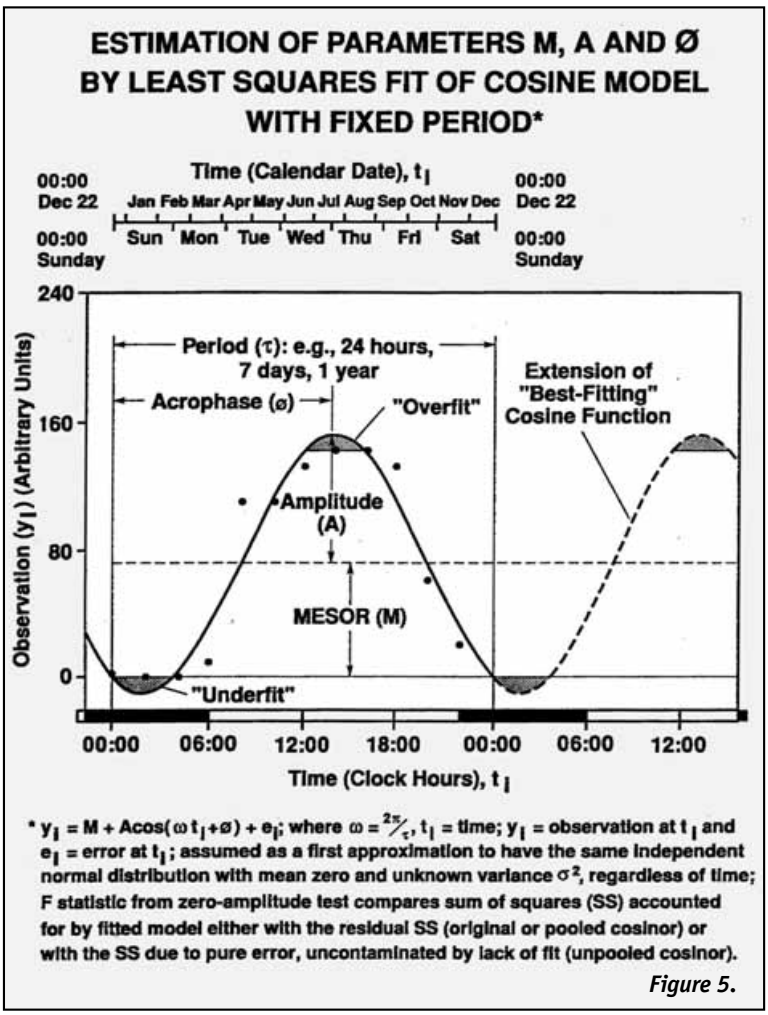

Figure 5.

on the average 2%. Many possibilities were considered in the attempt to solve this puzzle. Concerns of overcrowding and bad ventilation in the wards of the hospital clinic and some ill-defined atmospheric-telluric influences, a puerperal miasma or what was called the "genius epidemicus" were all considered. There was even the notion that the women were dying of shame because examinations by male medical students offended their sense of propriety.

This was the thinking at the time when the difference in mortality at the two clinics became a concern of Ignaz Semmelweis. He had been trained by the pathologist Rokitansky and had observed the ravages of puerperal fever on the organs of many pregnant women. The solution came to Semmelweis when his friend and teacher Jacob Kolecka died of sepsis; during an autopsy a student's scalpel had pricked Kolecka's finger. When Semmelweis compared the autopsy report of Kolecka with his experience at autopsies of maternity cases, he made the connection: the student's knife, previously infected by use on a cadaver, had killed Kolecka. In the same way the fingers of students and physicians spread fatal infections to the maternity cases, since they had done autopsies just before they examined the women in the delivery room, and the usual soap-and-water washing of hands was not a sufficient precaution. Thus Semmelweis solved the riddle of the difference in mortality between 1) the obstetrical clinic, where the

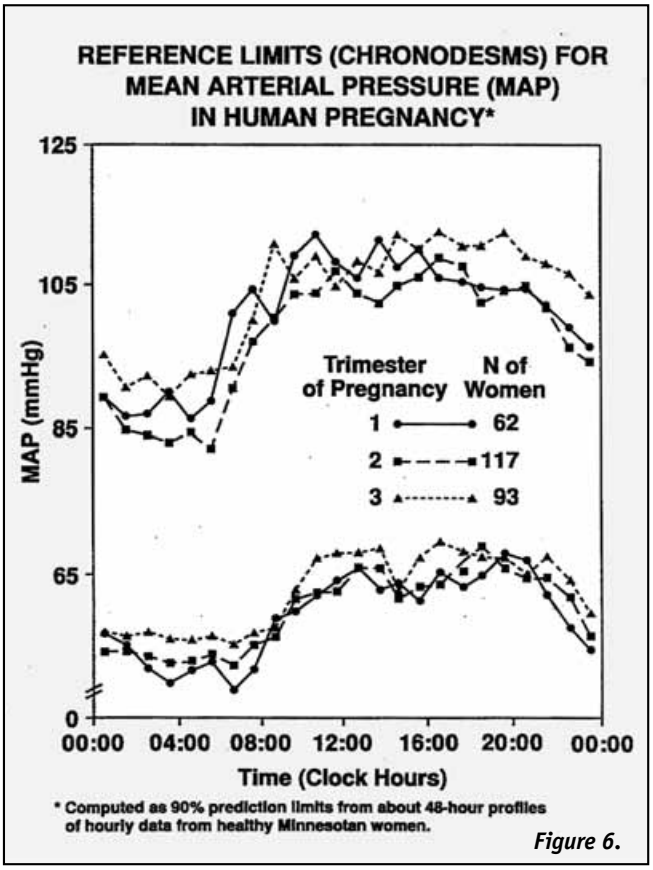

Figure 6.

Figure 5. Characteristics of rhythms. Least-squares fit by cosinor of a 24-hour cosine curve yields estimates for the MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), a rhythm-adjusted mean; the double amplitude, a measure of the extent of predictable change within a cycle, and of the acrophase, a measure of the timing of overall high values recurring in each cycle. © Halberg.

Figure 6. Circadian stage-specified reference limits (chronodesms) of mean arterial pressure (MAP) in the first, second and third trimesters of pregnancy, computed as 90% prediction limits. Limits derived from data obtained from healthy Minnesotan women, each providing an about-48-hour profile of hourly data. In any one trimester of pregnancy, the changes as a function of circadian stage far exceed those due to gestational age. © Halberg

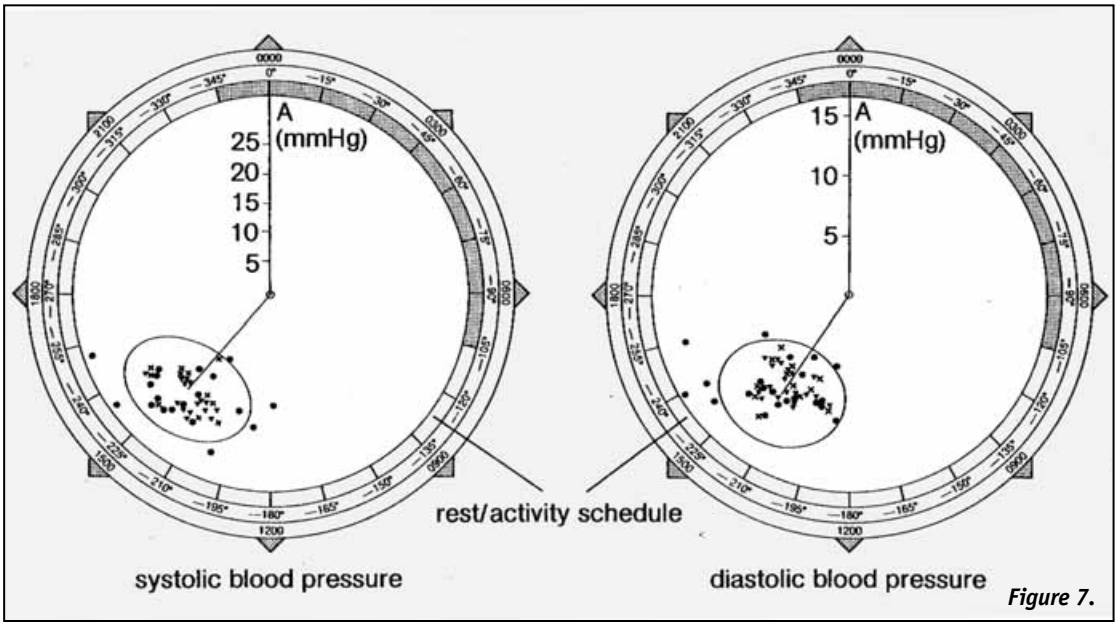

Figure 7. Distribution of individual amplitude-acrophase (A,ϕ) estimates of systolic and diastolic blood pressure of clinically healthy woman in 90% reference region computed from (A,ϕ) estimates over consecutive 2-day intervals. Sampling for at least 2 days represents a step in the right direction toward a technical reliability of the circadian characteristics, since all amplitude-acrophase pairs from spans covering at least 2 days happen to be inside a 2-day reference region, whereas 33% or 28% of the parameter pairs derived from 1-day spans are outside this region for systolic and diastolic blood pressure, respectively. (A,ϕ) estimates from 1-day intervals (•, 33 or 28% outside), 2-day intervals (x, all inside) and ≥2-day intervals (▼, all inside). These technical aspects of the sampling requirements, on just one clinically healthy woman, indicate the great gain from extending the current 24-hour monitoring profile by another 24 hours, rather than restricting it, e.g., to 6 hours (Sheps and Canzanello, 1994), whereby a circadian amplitude cannot be estimated at all. On 23 other patients conventionally diagnosed as "normotensive", the diagnosis based on 4 and an added 2 days of monitoring was not consistent with that obtained during an additional 3 days (Halberg and Cornélissen, 1995). For these and many other reasons (Halberg, 1988), 7-day monitoring is advocated as a routine procedure. © Halberg.

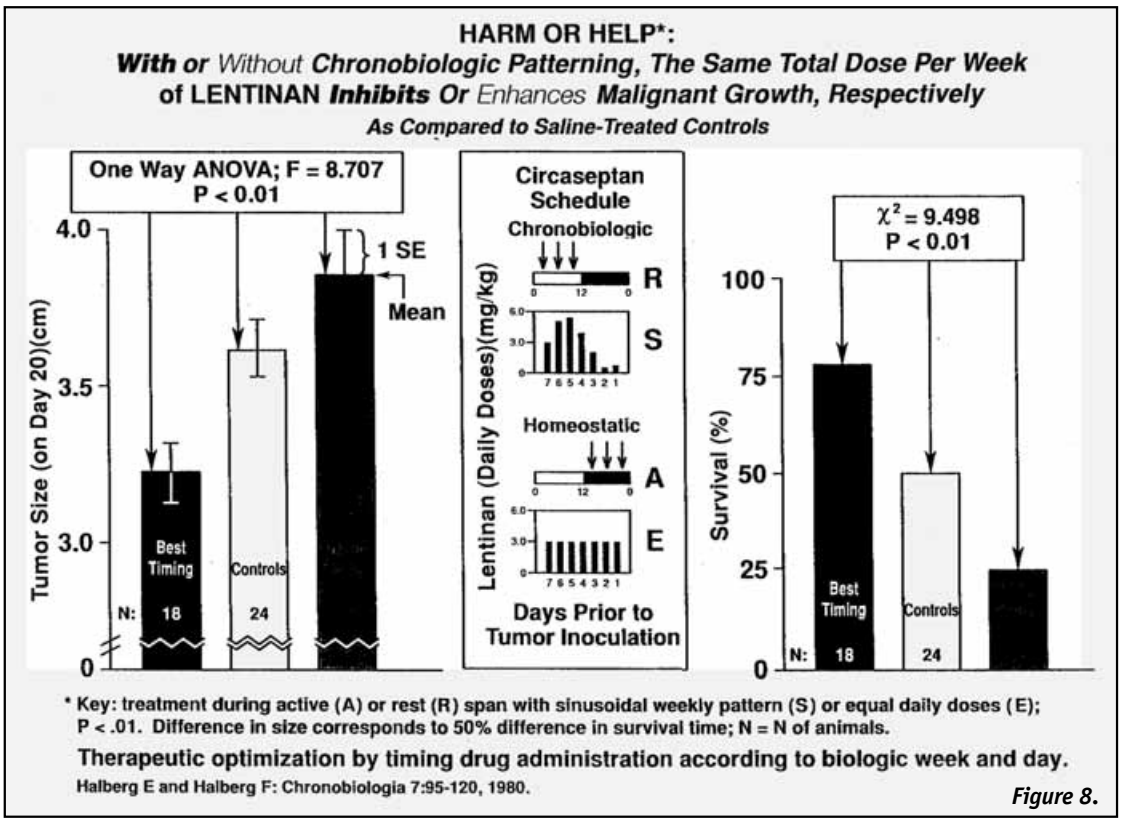

Figure 8. The same total dose of the same molecule, lentinan, depending on the circadian and circaseptan patterns of its administration, stimulates vs. inhibits the growth of a malignancy. © Halberg.

mothers-to-be were examined by students who often went directly to the maternity wards from the morgue, and 2) the clinic staffed by traditional midwives, whose duties did not involve autopsies.

At the end of May 1847 Semmelweis introduced disinfection of the hands with chlorine into the first obstetric clinic. By June, the mortality percentage had dropped sizably, and by November 1847 it was 2.55%. The truly great physicians of his time, Skoda and others, immediately recognized the impact of Semmelweis' discovery and supported him unreservedly. Unfortunately, the administrators of Semmelweis' institution did not. Semmelweis' position was discontinued in March 1849. He had difficulties thereafter as well. The prestigious French National Academy of Medicine in Paris rejected his claim. He then wrote his masterwork on "The etiology, concept and prophylaxis of puerperal fever" and began his lonely crusade. Eventually, it fell to Sir Joseph Lister, who in 1867 published "On the antiseptic principle in the practice of surgery", to finally influence the medical profession to adopt thorough antiseptic practices.

20th century scenario

With the historical background in mind, over 17 years ago, a keynote lecture at a prestigious Capri symposium, introducing the first drug (Dutimelan 8 15) which carried timing in its name, Figure 4 (Carandente and Halberg, 1991), was entitled "Protection by timing treatment according to bodily rhythms: an analogy to protection by scrubbing before surgery" (Halberg, 1974). Superficially, scrubbing has nothing to do with chronobiology, except perhaps that recognition of the need for antisepsis, like that for timing, was extremely slow.

The present generation of patients and their physicians is benefiting from the availability of hygiene and antibiotics. For them, fortunately, the horror of wound infections in the pre-sulfonamide, pre-penicillin era is at best history. History, however, repeats itself, as it does in regions devoid of any antiseptic supplies, with extreme, grimy destitution and famine. Such horrible contemporary mementos of a not-so-distant past notwithstanding, too many are apt to forget how long it took for antisepsis to be accepted. Many amputations had to be done both on limbs because of gangrene and on attitudes that had to be overcome: ignorance and, once this was overcome, inertia. The times are still difficult for advocates, if not of the prevention of wound infections, then for those of chronobiology in the context of the scenario of the case report (Cornélissen et al., this issue) and others (Cornélissen et al., 1996), even in the university where this science reportedly originated (Waterhouse and Åkerstedt, 1998).

Entrenched attitudes are not easy to change. For too long, the suggestion to scrub was not heeded. Today it would be criminal negligence to fail to scrub before surgery. One of us (FH) along similar lines, many years ago, addressed the U.S. Food and Drug Administration (FDA) under the title "Ignorance, indolence; when will it become criminal negligence?" A commissioner of the FDA who greeted the speaker as an apparent dear friend, once alone with his staff told them to return to "business as usual", as we were told by the late John Harter, who, unknown to the commissioner, was a chronobiologist himself (he had introduced alternate-day corticosteroid therapy). Admonitions to take chronobiology into account and to exploit it much more often fall on deaf ears. Both the merit of antisepsis over a century ago and that of chronobiology were presented at prestigious meetings, including academies of medicine. Proponents of chronobiology have become academicians. Nonetheless, this new discipline is taking a very long time to penetrate actual health care practice. The explanation may not be difficult.

Cleanliness before surgery, a much simpler concept, after Averroës had to wait eight centuries for Lister before it became antisepsis. The quite conclusive and dramatic evidence of Semmelweis went unheeded for a long time. Semmelweis stepped on many toes. He did not live to see the full acceptance of antisepsis.

The resistance against chronobiology is also great. Chronobiologists cannot help but, by their mere presence, remind the establishments throughout medicine of *e pur si muove* (Cornélissen et al., 1989). It matters little whether Galileo actually muttered "nevertheless it [the earth] does move" as he left the Inquisition. It matters greatly for a scientific health care that we exploit the information within the physiologic range. We must do so before we become ill; we must overcome the inquisition of those teaching the "wisdom of the body" and the relative constancy of our internal milieu. Homeostasis sanctions limitation of our activities to office hours 5 days a week. Chronobiology is much more demanding.

By 1939, Jores, subsequently co-founder of the Society for the Study of Biologic Rhythms (now the International Society for Chronobiology), eventually its president and also president of the German Society of Internal Medicine and Endocrinology, confronted with the suggestion to treat at meal times, referred to "this idiocy of *three times a day"*. The merits of compliance by drug use at meal times notwithstanding, Gross in 1985 again preferred a time-targeted treatment. He realized the need for a time-microscopic assessment of a variable such as blood pressure for a time-specified diagnosis. Along the scale of 24 hours, systolic pressure changes on the average by over 60 mm Hg and diastolic by over 50 mm Hg each day (Halberg et al., 1984, 1988; Cornélissen, 1987). Gross also emphasized that it does not suffice to look at a curve on a graph or at a series of tabulated numbers in order to discuss the dynamics of blood pressure. The reactions to different stimuli have to be somehow separated from a basic statistically validated rhythm, gauged by some inferential statistical analyses for some reproducible features that characterize everybody, Figure 5 (Halberg, 1969).

To turn back to hygiene, eventually, attention to scrubbing has saved many lives in the delivery and

operating rooms broadly. Many more lives, as well as horrendous suffering and enormous costs, may be saved if the mere risks of developing illness are detected early by an alteration of rhythm parameters, which may occur before the earliest signs of disease appear. A variable such as blood pressure can well show mean values within a "physiologic range", yet the dynamics of the variable are altered to an extent that they should and can be acted upon preventively. This is the more important since blood pressure deviations concern a large segment of the population and since blood pressure can be readily self-measured, although it is preferably automatically recorded.

In clinically healthy men and women, in the latter during pregnancy as well, "research in practice" has yielded invaluable new usual value ranges, chronodesms, specified by clock-hour and, when pertinent, by gestational age. Chronodesms have already been mapped in Minnesota and can be used for the interpretation of single samples (Figure 6). Concurrently, reference intervals for a parameter pair, namely the amplitude and acrophase, measures of the extent and timing of predictable since rhythmic change are also available (Figure 7). On the basis of a statistically significant alteration, warnings can be found and given for timely intervention whenever deviations from chronobiologic dynamic norms occur.

Conclusion

"Circadian" was called "Halberg's paranoia" before it was defined in the Oxford English Dictionary (1972) and the Britannica Medical and Health Annual (Waterhouse and Åkerstedt, 1998). In the interim, the broader time structure has revealed that timing can make the difference between stimulating and inhibiting DNA labeling (Walker et al., 1985). The same dose of the same immunomodulator can stimulate or inhibit the growth of an immunocytoma, as a function only of its timing (Halberg E. and Halberg F., 1980), Figure 8. Even more important are disease risk syndromes that lead to the prevention of stroke and other catastrophic events (Halberg et al., 1998).

Most important is the need to introduce chronobiologic literacy, matching the ability to read and write. Learning the "3 R's" is expensive, time-consuming, and complex, as is the addition of the fourth "R", rhythmometry (Halberg et al., 1973). In ancient Rome, those who needed a letter written went to a scribe. One of us had a surprise in asking about the extent of illiteracy in Siberia while consulting about its health services. Literacy was virtually 100%, and there was also lively interest in acquiring the fourth "R", i.e., chrono-literacy for instrumented self-help.

The pacemaker firm Medtronic (Minneapolis, Minnesota, USA) had as its motto "Restoring man's full life" (Cornélissen et al., 1999). The "Medical Alley" of Minnesota (and/or other sites as well) can gain a new dimension in this context. A better molecular, i.e., chrono-molecular science, is needed. Even more urgently needed is a health care utilizing the telemetry already available for laboratory animals as small as mice, that could be made available to humans once the need for it is recognized.

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