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Hurdles to asepsis, universal literacy, and chronobiology—all to be overcome

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Abstract

A joining of chronobiology and endocrinology was achieved in 1974 at a symposium focusing on the critical role of the hypothalamic-pituitary-adrenal network on the basic side and on the first drug to carry timing in its name. The next step is a section on chronobiology in this neuroendocrinology journal. An account of the problems encountered before both asepsis and universal literacy became the law of the profession and of the land serves here as background to endeavors in behalf of chronobiologic literacy. A step toward the latter goal is the use of systematically collected measurements of heart rate and blood pressure evaluated by computer against reference standards from peers of corresponding age, gender and ethnicity. Thereby, an illustrative, clinically relevant aspect of everyday physiology is resolved within the otherwise neglected normal range, and disease risk syndromes are detected so that preventive treatment can be instituted before catastrophic disease occurs. The scope of this chronobiology section of the Neuroendocrinology Letters is to map the time-qualified feedsideward interactions within the neuroendocrines, in the rest of an organism and in the environment. Thereby, we replace time-unqualified feedbacks and feedforwards, along imaginary axes, by neuroendocrine and cellular networks operating predictably insofar as rhythmically within the range of everyday physiology. Subtle effects are thus found that are otherwise covered by the curtain of ignorance drawn over the normal range. More important, feedsidewards account for opposite effects that recur rhythmically, and thus help clarify mechanisms that may underlie the difference between stimulating or inhibiting a malignancy and thus shortening or lengthening the lifespan.

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THE STORY BEHIND

Scrubbing[1]

In the twelfth century CE, in Cordova, Spain, 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 Rabbi 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 before the resolution of bacteria by the microscope gave it a rational basis. Today, hygiene generally and scrubbing involve very many aspects of medicine.

It appears that the history of puerperal fever in the mid-19th century has several parallels in the status quo of the use of chronobiology in current health care. By 1843, the contagious nature of "childbed fever" had already been recognized by Oliver Wendell Holmes (1809–1894), the noted American author, teacher and practitioner of medicine. Yet a matter as cut-and-dried as antisepsis continued to be ignored by the medical establishment of that day.

In 1784 the Austrian Emperor Joseph II founded an obstetrical clinic at the General Hospital in Vienna, 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 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 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. Semmelweis 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!"

Unfortunately, the administrators of Semmelweis' institution were not so supportive. Semmelweis' position was discontinued in March 1849. He had difficulties thereafter as well. The 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.[2] 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.

But for a long time Holmes, Lister and Semmelweis were ridiculed by surgeons in the English-speaking world who continued to operate in street clothes

and refused to change their blood- and tissue-splattered clothes between procedures—an attitude equivalent to taking *the* (casual) blood pressure. According to the celebrated Victorian physician Sir Frederick Treves (cited by Gordon in [1]), it was considered to be as "finicking and affected" for surgeons to be clean before procedures intended to save lives as it would have been for an executioner to trim his nails before beheading a condemned prisoner! "Only" puerperal fever was at stake (it seems finicky, by analogy, to insist on a weeklong blood pressure profile since "only" stroke is at stake.) Sutcliffe and Duin [2] in turn note that Holmes was criticized by eminent surgeons for having the temerity to suggest that the hands of them and their gentlemen colleagues were unclean; Holmes retorted that "Medical logic does not appear to be taught or practiced in our schools." Adams [3] adds with keen irony: "Doctors in the 1780s ... complained about *midwives with dirty hands* [emphasis ours] poking around in the mother's innards during labor. Truth is, as long as it was just midwives doing the poking, sterility wasn't that important. Only when doctors got involved did it become a matter of life and death."

Today, strokes and other cardio-, nephro- and vascular diseases are on the line, and it is mere common sense to exercise precaution. We must distinguish, as Jay Cohn put it, between risk contributors and risk markers, by operational quantitative assessments, and as we have separated risk and other markers in a glossary based on data [4, 5]. It was not evangelism to ask surgeons to scrub before they operate. In line with Janeway [6], it is neither finicking nor far out to offer monitoring on a citywide basis to residents before they are seen as patients.

The ethics of doing a 24-hour or even a 6-hour measurement profile, as is done at the Mayo Clinic [7], vs. doing a surveillance for 7 days as a start and for longer and as long as is necessary in the given case, notably in the case of an abnormal blood pressure, is the issue [8]. As a minimum we must not presume to rule out a deviant blood pressure by a single measurement because we may thereby fail to recognize not only **c**ircadian **h**yper-**a**mplitude-**t**ension, or CHAT, but high blood pressure in itself. In support of that point is the finding that when one measures dozens of people, each at 15-minute intervals for 7 days, one will hardly find any hypertensives who do not have normotensive values during office hours, and hardly any normotensive who will not have hypertensive values during office hours [9]. A patient of Bartter [10] had one diagnosis from another physician he saw in the morning and another diagnosis from a another physician he saw in the afternoon, hypertension vs. normotension, respectively, dependent only on the time of day. This point becomes obvious in an impeachment of current practices, showing, in an abstract way, how patients have to be necessarily hypertensive in the afternoon and normotensive in the morning, if they are rhythmic around certain common operating means—and who is not rhythmic [11]?

As far back as 1913, Percival Nicholson [12] was recommending that blood pressure should be taken at the same time each day. Nicholson thus forced recognition of chronobiological variations. This was a step in the right direction, better than taking **the** blood pressure at **any** convenient time, a precaution needed for single measurements but not sufficient. Janeway in 1904 [6] did this much better:

> The diurnal variations, including the effects of eating and sleep, must be in mind. In following cases from day to day, especially with reference to the effects of treatment on the blood pressure, determinations should be made at the same hours. …
>
> Everyone admits the importance of this [variability along the 24-hour scale] in studying the course of the temperature in disease. With arterial pressure, it is not a whit less important. …
>
> … *it is essential* that a record of the pressure be made at frequent intervals *at some time previous* [presumably to an examination], to establish the *normal level* and the *extent of the periodic variations*. When this is done, it may be possible to demonstrate changes of small extent, which, lacking this standard for comparison, would be considered within the limits of normal variation. (Italics ours.)

The fourth "R": rhythm (chronobiologic) literacy

The proposal to introduce the teaching of chronobiology with that of the alphabet; to learn biology with one's own body as the laboratory; and to learn mathematics by the analysis of self-measurements has repeatedly been tested in Minnesota [13–19], Arkansas [20], Connecticut [21] and Italy [22]. In the U.S., the National Science Teachers Association has published a textbook on the topic [23] and educators have introduced the issue to legislators [24]. There is no battle analogous to that reviewed below for acceptance of universal literacy, but there is inertia and neglect rather than resistance to the proposition of encouraging self-help by active education and the provision of instrumentation as a public service [13]. We next review the battle that indeed occurred

in the case of universal literacy. It may seem beyond our scope herein to describe the tribulations of those who sought to introduce the fourth "r" [17]. Instead, we turn to historical facts. Those in a hurry may proceed to the next section, "Urban healthwatch."

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The need for universal literacy was recognized only slowly, and the same difficulty confronts chronobiologic literacy today. The Massachusetts Educational Law of 1642 decreed that "in euery towne the chosen men appointed for managing the prudential affajres … shall have power to take account from time to time of all parents and masters and of their children … especially of their ability to read …". The Massachusetts Educational Law of 1647 ordered "that every towneship in this iurisdiction, after the Lord hath increased them to the number of 50 housholders, shall then forthwith appoint one within their towne to teach all such children as shall resort to him to write and reade …" [25]. The Massachusetts Educational Law of 1648 goes further and imposes sanctions, as might be done to assure as yet not chronobiologic literacy:

> *Forasmuch as the good education of children is of singular behoof and benefit to any Common-wealth; and whereas many parents and masters are too indulgent and negligent of their duty in that kinde* [italics in original]. It is therefore ordered that the Select men of everie town, in the severall precincts and quarters where they dwell, shall have a vigilant eye over their brethren and neighbours, to see, first that none of them shall suffer so much barbarism in any of their families as not to indeavour to teach by themselves or others, their children and apprentices so much learning as may inable them perfectly to read the english tongue, and knowledge of the Capital lawes; upon penaltie of twentie shillings for each neglect therin. [25]

On the other hand, a generation later, Sir William Berkeley, royal governor of the colony of Virginia, informed the Committee of Plantations in London: "I thank God, there are no free schools, nor printing; and, I hope, we shall not have, these hundred years. For learning has brought disobedience, and heresy, and sects into the world; and printing has divulged them and libels against the best government: God keep us from both!" [26].

Efforts by English humanitarians from early in the eighteenth century to teach the children of the poor to read by means of "charity schools" aroused strong opposition. Conservative opinion held, in general, that the ability to read would make workers discontented and thus foster social unrest [27]. The aristocratic position was set forth with great force and clarity by Bernard Mandeville, a physician of Dutch origin, in *The Fable of the Bees* [28]. F.B. Kaye, editor of the standard edition of the *Fable,* summarizes Mandeville's case against the charity schools:

> Nobody will do unpleasant work unless he is compelled to by necessity. There is, however, "Abundance of hard and dirty Labour" to be done. Now, poverty is the only means of getting people to do this necessary work: men "have nothing to stir them up to be serviceable but their Wants, which it is Prudence to relieve, but Folly to cure." National wealth, indeed, consists not in money, but in "a Multitude of laborious Poor." Since, therefore, it would be ruinous to abolish poverty, and impossible to do away with unpleasant labour, the best thing to do is to recognize this fact, and help adapt the poor to the part they have to play. But charity-schools, by educating children above their station and thus leading them both to expect comforts they will not have and to loathe occupations they must engage in, are subversive of the future happiness and usefulness of the scholars:
>
> … to divert … Children from useful Labour till they are fourteen or fifteen Years old, is a wrong Method to qualify them for it when they are grown up.

Finally, he attacked the schools on the ground that they interfered with the natural adjustment of society:

> … proportion as to Numbers in every Trade finds it self, and is never better kept than when no body meddles or interferes with it.

The gusto of Mandeville's assault on the charity-schools, and his incidental attack on what he termed the "Petty Reverence for the Poor," is apt to impress the modern reader as almost incredibly brutal. But that is because the *Essay* is judged from a humanitarian point of view that hardly existed in Mandeville's time. Seen in historical perspective, there is nothing unusually harsh in Mandeville's position. The age was not interested in making the labourer comfortable, but in making his work cheap and plentiful. Sir William Petty was no friendlier than Mandeville to the poor when he termed them "the vile and brutish part of mankind"; even so ardent an upholder of the rights of man as Andrew Fletcher urged that labourers be returned to a condition of slavery; and Melon, too, advised slavery. The truth is that, although Mandeville's attack on the charity-schools caused great scandal at the time, his adversaries were really as little desirous as Mandeville to lessen the labourer's work or raise his wages.

Mandeville, indeed, was perhaps more considerate of the condition of the labourer than was the average citizen, for he felt at least the need of answering what could be urged on the other side:

> I would not be thought Cruel, and am well assured if I know anything of myself, that I abhor Inhumanity; but to be compassionate to excess where Reason forbids it, and the general Interest of the Society requires steadiness of Thought and Resolution, is an unpardonable Weakness. I know it will be ever argued against me, that it is Barbarous the Children of the Poor should have no Opportunity of exerting themselves, as long as God has not debarr'd them from Natural Parts and Genius more than the Rich. But

> I cannot think this is harder, than it is that they should not have Money as long as they have the same Inclinations to spend as others.

It should be remembered, also, that Mandeville believed the lot of the hard-working poor need not be a sad one:

> *Was impartial Reason to be Judge between real Good and real Evil, … I question whether the Condition of Kings would be at all preferable to that of Peasants, even as Ignorant and Laborious as I seem to require the latter to be. … what I urge could be no injury or the least diminution of Happiness to the Poor … by bringing them up in Ignorance you may inure them to real Hardships without being ever sensible themselves that they are such.*

In view of this apology and the fact that his views rested on the current economic attitude, such complaint as was made against his brutality may be taken as due really to his having omitted the flavouring of sentiment and moralizing with which his contemporaries sweetened their beliefs; they were scandalized at his downrightness of statement, which here, as elsewhere, was able to make a current creed obnoxious by the mere act of stating it with complete candour.

It is particularly regrettable that such views were offered by a physician. Similar opinions, often cloaked in various rationalizations, continued to be expressed for well over a century. The following quotations from Mandeville's "Essay on Charity, and Charity-schools" (an integral part of the rather curious structure of the *Fable)* are perhaps pertinent:

> The Welfare and Felicity therefore of every State and Kingdom, require that the Knowledge of the Working Poor should be confin'd within the Verge of their Occupations, and never extended (as to things visible) beyond what relates to their Calling. The more a Shepherd, a Plowman or any other Peasant knows of the World, and the things that are Foreign to his Labour or Employment, the less fit he'll be to go through the Fatigues and Hardships of it with Chearfulness and Content.
>
> Reading, Writing and Arithmetick, are very necessary to those, whose Business require such Qualifications, but where People's livelihood has no dependence on these Arts, they are very pernicious to the Poor, who are forc'd to get their Daily Bread by their Daily Labour. Few Children make any Progress at School, but at the | same time they are capable of being employ'd in some Business or other, so that every Hour those of poor People spend at their Book is so much time lost to the Society. Going to School in comparison to Working is Idleness, and the longer Boys continue in this easy sort of Life, the more unfit they'll be when grown up for downright Labour, both as to Strength and Inclination. Men who are to remain and end their Days in a Laborious, Tiresome and Painful Station of Life, the sooner they are put upon it at first, the more patiently they'll submit to it ever after. (...)
>
> No Body will do the dirty slavish Work, that can help it. I don't discommend them; but all these things shew that the People of the meanest Rank know too much to be serviceable to us. Servants require more than Masters | and Mistresses can afford, and what madness is it to encourage them in this, by industriously increasing at our Cost that Knowledge which they will be sure to make us pay for over again! And it is not only that those who are educated at our own Expence incroach upon us, but the raw ignorant Country Wenches and Boobily Fellows that can do, and are good for, nothing, impose upon us likewise. The scarcity of Servants occasion'd by the Education of the first, gives a Handle to the latter of advancing their Price, and demanding what ought only to be given to Servants that understand their Business, and have most of the good Qualities that can be required in them. (...)
>
> Abundance of hard and dirty Labour is to be done, and coarse Living is to be complied with: Where shall we find a better Nursery for these Necessities than the Children of the Poor? none certainly are nearer to it or fitter for it. Besides that the things I called Hardships, neither seem nor are such to those who have been brought up to 'em, and know no better. There is not a more contented People among us, than those who work the hardest and are the least acquainted with the Pomp and Delicacies of the World.

Although such influential figures as Addison and Steele supported the charity-school movement [29], opposition similar to Mandeville's lasted a long time. Soame Jenyns, for example, an influential politician, declared in 1757 that ignorance is "the appointed lot of all born to poverty and the drudgeries of life … the only opiate capable of infusing that sensibility, which can enable them to endure the miseries of the one and the fatigues of the other … a cordial, administered by the gracious hand of providence, of which they ought never to be deprived by an ill-judged and improper education" [27].

In the United States, the New England attitude (but with political rather than religious motivation) spread rapidly throughout the North and Northwest after the Revolution, and by the 1830s a campaign for the establishment of universal free public education was gaining momentum in all the free states. Official American ideology held that the population at large must be educated in order to cast its ballots intelligently. The leading propagandist for free public schools, Horace Mann, added a broader conception of democracy to the merely political case for public schools. In his *Twelfth Annual Report … as Secretary of Massachusetts State Board of Education* (1848) Mann included a typical statement of his case:

> According to the European theory, men are divided into classes,—some to toil and earn, others to seize and enjoy. According to the Massachusetts theory, all are to have an equal chance for earning, and equal

> security in the enjoyment of what they earn. The latter tends to equality of condition; the former, to the grossest inequalities. Tried by any Christian standard of morals, or even by any of the better sort of heathen standards, can any one hesitate, for a moment, in declaring which of the two will produce the greater amount of human welfare, and which, therefore, is more conformable to the divine will? …
>
> Now surely nothing but universal education can counterwork this tendency to the domination of capital and the servility of labor. If one class possesses all the wealth and the education, while the residue of society is ignorant and poor, it matters not by what name the relation between them may be called: the latter, in fact and in truth, will be the servile dependents and subjects of the former. But, if education be equally diffused, it will draw property after it by the strongest of all attractions … Education then, beyond all other devices of human origin, is a great equalizer of the conditions of men,— the balance wheel of the social machinery. … It does better than to disarm the poor of their hostility toward the rich: it prevents being poor [30].

Although the need for at least rudimentary literacy in the populace at large was an evident corollary of universal manhood suffrage, support of free schools by tax revenues encountered some resistance in the United States. Various arguments were advanced in opposition, but the ultimate basis of opposition was for the most part similar to Mandeville's. Merle Curti summarizes opposition to tax support for public education in the mid-nineteenth century as follows:

> Free school laws, it was argued, merely filled the bellies and covered the backs of the indigent at the expense of the taxpayer; what could be more patent than the certainty that if free schools were granted, the concessions would not end short of socialism itself ? To provide free schooling for the less well-to-do would result in the loss of their self-respect and initiative; it would, in brief, pauperize them. Some argued that free public schools must be opposed on the ground that they would provide education to those "who were better suited to their station without it". Educated workmen, contrary to the arguments of the friends of the public school, were not, it was argued, a necessity. On the contrary, so the contention was, prosperity depended rather on an abundant supply of labor "comparatively uneducated" [31].

There was also a deep-seated anti-intellectualism among uneducated backwoodsmen that is expressed in brilliantly comic form by the monologue of Huck Finn's Pap. When he hears that Huck has been "adopted" by a well-disposed widow and sent to school for the first time in his life, Pap says:

> You've put on considerble many frills since I been away. I'll take you down a peg before I get done with you. You're educated, too, they say; can read and write. You think you're better'n your father, now, don't you, because he can't? *I*'ll take it out of you. Who told you you might meddle with such highfalut'n foolishness, hey? … you drop that school, you hear? I'll learn people to bring up a boy to put on airs over his own father and let on to be better'n what *he* is. … Your mother couldn't read, and she couldn't write, nuther, before she died. None of the family couldn't, before *they* died. *I* can't; and here you're a-swelling yourself up like this. … if I catch you about that school I'll tan you good [32].

Opponents of racial desegregation continued to oppose free public education for blacks into the later nineteenth century [33]. It was even argued at one point that "the negro who cannot read and write is more moral than one who can …" [34]. And covert attitudes of this sort only slowly fade beneath the surface of the debate over desegregation of American education in the twentieth century. The plan for the Roseville blood pressure and heart rate project, which touches on public health as well as education, is a step in the twenty-first century toward a more ambitious goal.

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Urban healthwatch?

Focus on alteration in pattern requires a change in attitude, as was needed for the case of universal literacy in some, but not all parts of the world. It first appears to be hyperbole when we advocate seven-day around-the-clock blood pressure and heart rate monitoring, hoping that we figuratively seek to lead horses to water who are willing to drink.

Disease risk syndromes can be documented by monitoring blood pressure and heart rate at 1-hour or shorter intervals for 48 hours on groups in research [35–40], and on individuals for 7 days, or longer, if need be. Risk syndromes can be assessed by classical statistical endpoints such as a 24-hour (circadian) standard deviation of blood pressure and heart rate and by cosine curve-fitting [41]. Thereby, the pattern of any multifrequency rhythms constituting an even broader time structure or chronome is resolved with as many components as the density and length of the data series permit. The endpoints from curve fitting or parameters include the MESOR (**m**idline-**e**stimating **s**tatistic **o**f **r**hythm), the amplitude and acrophase of any fundamental 24-hour component (measures of the extent and timing of reproducible variability, respectively), and the amplitude and acrophase of each harmonic of the circadian variation needed to describe the waveform. A dividend from curve-fitting is that the MESOR is a more precise and more accurate estimate of location than the arithmetic mean. Non-parametrically, excess pressure can be detected by replacing the conventional straight line for the upper limit of an

acceptable blood pressure (and heart rate) by one that takes circadian variations into account. The area under the blood pressure data plotted as a curve, where this curve exceeds a time-varying limit and that limit itself, is the hyperbaric index [40–42].

By these procedures, a sphygmochron is obtained, as a summary of a monitoring profile, over time, involving computer-implemented comparisons with reference values from peer groups (available for analyses, carried out at the Chronobiology Center of the University of Minnesota; if interested contact by e-mail corne001@tc.umn.edu). Thereby, a change in the pattern of variability, indicating a very high risk of stroke, can be picked up [36, 38, 40, 41]. Sometimes, this risk occurs only within the range of everyday physiology. A very high risk of kidney disease as well as stroke is found in association with too large a circadian amplitude in the 24-hour pattern of blood pressure [36, 38], and/or with otherwise altered patterns such as a shift in the timing of variation. In this context, a change in the circadian amplitude of blood pressure is a more sensitive index than non-dipping [36, 43]. A decrease in the extent of heart rate variability below a threshold is also a marker of an elevated risk of stroke and other catastrophic vascular events [39, 44]. To avoid threshold-dependent conditions, surveillance of both the variability and average of blood pressure and heart rate is suggested

1. because a feature of variability, such as circadian blood pressure overswinging, called **c**ircadian **h**yper-**a**mplitude-**t**ension (CHAT), can be detected only by systematic focus on variability, preferably implemented by automatic instrumentation and analyses, which are both affordably available for research in actual practice;
2. because circadian blood pressure overswinging is associated with a greater risk of stroke than an elevated average blood pressure; and
3. because the average blood pressure, the proven etiopathogenetic factor of vascular catastrophic disease, can be more reliably estimated with a systematic account for variability than by a spot-check.

The association with catastrophic disease renders the assessment of variability and of the improved average of blood pressure into a community concern. We all pay, indirectly if not directly, for the care of massive strokes, myocardial infarctions or nephropathy, apart from the immeasurable suffering and disability of those afflicted. In Minnesota, Dan Wall—an attorney, the immediate past mayor of Roseville, a suburban city of about 35,000 residents, and an author himself [45]—succeeded in acquiring for his constituents at first ten automatic ambulatory instruments for 24-hour/7-day blood pressure and heart rate monitoring, as yet only slightly obtrusive tools. The incumbent mayor who succeeded him is in agreement with the plan and, despite his youth (28 years of age), intends to start monitoring himself and his wife. A project such as that planned originally by attorney Wall is a challenge second to none to the engineering profession and industry more generally to build new, further miniaturized instrumentation that will help to greatly improve the quality of care while further limiting its cost, which is already greatly reduced.

A public service task of physiological monitoring is, we trust, within the mandate of those not only in local but also in federal government agencies dispensing resources, and is just a first step toward education in a much broader chronobiologic literacy. We append a handout to these lines for use in health care offices and in public spaces and a memorandum for those who wish to participate in this (research in) practice. Unquestionably, the investment into a very slight discomfort wearing the instrumentation is dwarfed by picking up the warning of a massive stroke.

Brochure proposed for the general public, originally produced for the city of Roseville, Minnesota, as a general informational handout

HEALTHWATCH

Why 7-Day/24-Hour Blood Pressure Monitoring? What you may want to know about blood pressure
Prepared at the Chronobiology Center of the University of Minnesota, with help by Earl E. Bakken, Founder of Medtronic Inc., Fridley, Minnesota (now President, North Hawaii Community Hospital Inc., Kamuela, Hawaii) and Patrick Delmore, Head, Communications, Medtronic Inc., Fridley, Minnesota.

Summary

The usual way of measuring and interpreting blood pressure can be substantially improved. “Casual” blood pressure readings taken in a doctor’s office or drug store can be misleading. Measurements taken occasionally can be unusually high or low; false positive and false negative diagnoses can occur. False positive diagnoses can lead to unneeded treatment, unnecessary concern, expense and side effects from medications, such as cough, cardiac arrhythmia or

impotence. People who actually need treatment can be lulled into a false sense of well-being by occasional or mostly "good" blood pressure readings and may suffer a stroke or heart attack that could have been prevented. Moreover, the technically best single measurements will miss an altered pattern of variability that a computer detects, even when the inspection of the actual measurements reveals hardly any values that are too high or too low. The change in extent of variation, such as overswinging of blood pressure or underswinging of heart rate, tells us about the greatest risk of stroke, even when each value appears to be "good", insofar as it is neither too high nor too low.

The use of fully automatic ambulatory blood pressure monitors—programmed to take measurements at preset intervals for at least one week, or longer, when analyzed chronobiologically—can help to make a more reliable diagnosis. These blood pressure readings (with added heart rate measurements) are directly transferred into computers for analysis according to chronobiology, the science of rhythmic and otherwise patterned changes in variability, called time structures or chronomes, resolved by computer as a standard deviation, a cosine curve or another objectively testable pattern.

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Variability as benefit

We're all born with natural variations in our circulation. Variations can also occur when we exercise physically and undergo excitement, anxiety or "stress". At the same time, we further respond to subtle factors in our environment, including the effect of storms in space (such as those causing the aurora borealis), an effect that can trickle down from extraterrestrial space to earth, to the poles and from there to lower latitudes. The development of borderline (and eventually of high) blood pressure is usually not accompanied by symptoms. The development of altered variability is much more often than not completely asymptomatic. Undesirable early changes in blood pressure variability pattern are difficult or impossible to discover and reliably ascertain without the collection of around-the-clock blood pressure measurements for at least 7 days. It is true that monitoring for two days rather than one, notably with a diary, is the greatest gain toward a reliable diagnosis. Each additional day, however, adds further to approaching the aim of avoiding a false diagnosis.

Even when blood pressure is very high on average, it can be a "silent disease". There may not be any symptoms until complications become apparent. These complications can include a stroke, a heart attack and kidney disease. It seems more reasonable to prevent blood pressure from becoming elevated or otherwise outside norms than it is to treat conditions resulting from an abnormal blood pressure pattern. Once high or otherwise abnormal blood pressure has damaged the heart, brain, kidney or other organs, major handicapping and fatal diseases are more likely to occur.

In the doctor's office, there's no way to obtain measurements around the clock. Yet modern instruments are available that collect readings while you sleep. And then they're analyzed by computer programs based on a data bank from thousands of individuals. The new hardware/software/data base provides new opportunities to treat a faulty blood pressure pattern (without or with medication) and thus prevent serious illnesses.

Results of 24-hour/7-day (24/7) blood pressure monitoring are interpreted by using special computer methods, developed at the Halberg Chronobiology Center at the University of Minnesota (733 Mayo Building, 420 Delaware St. S.E., Minneapolis, MN 55455; Tel: [612] 624-6976, Fax: [612] 624-9989, E-mail: halbe001@tc.umn.edu). Changes in blood pressure patterns can be detected as indicators of an elevated health risk, not apparent by using conventional methods.

Why monitoring?

The extent of suffering after a massive stroke is enormous and the healthcare costs related to high blood pressure are staggering—$30 billion in 1998 in the U.S. The ability to identify both those at risk and those with an already-elevated blood pressure reduces suffering and expense. It makes it possible to provide treatment early enough to prevent the actual development of an altered blood pressure pattern of variability as well as to lower a blood pressure that is already high or correct a blood pressure that is otherwise abnormal.

Your 24/7 blood pressure monitoring

The City of Roseville plans on offering—legalities permitting—24/7 blood pressure monitoring to all residents, from teenagers to seniors. If you decide to participate, you'll wear an only slightly obtrusive, and for those familiar with the load of self-measurement day and night, a reasonably comfortable, fully automatic, ambulatory blood pressure monitor for a week or more.

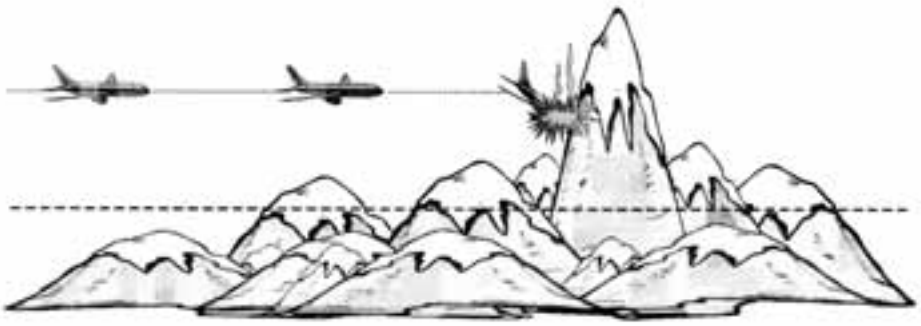
Why take blood pressure readings 24 hours a day?

Because in some people—possibly including you—relatively high blood pressures can occur at night rather than during the day. "Relatively" means that the pressures are high in relation to the range of acceptable pressures during rest and/or sleep. They may also be higher as compared to the range while you are awake and active. This altered timing of high and low pressures may happen spontaneously or in severe diabetes involving the autonomous nervous system, or because of long-acting blood pressure-lowering medications that cease acting sooner than anticipated. These high blood pressures will not be recognized in measurements taken only during the day.

Why take blood pressure readings 7 days a week?

Because abnormality can be there on some days but not on others. Fewer than 7 days of monitoring mean a greater chance of a false diagnosis.

Two features of the city's approach to blood pressure mon-



Cartoon illustrating the risk of CHAT (Circadian Hyper-Amplitude-Tension), a condition characterized by an excessive circadian blood pressure amplitude. Swings in blood pressure during rest and activity are healthy (left), but when they become too large, catastrophic events may ensue. © Halberg.

itoring make it highly effective.

First, your blood pressure can be automatically monitored with little interruption of everyday life. Except that you have to stand still when the cuff inflates and the monitor takes a measurement (you may be warned by a beep), you don't need to do anything special and you'll hardly know that the process is going on. This type of monitoring greatly reduces the likelihood of false readings and unnecessary treatment.

Second, your 24/7 blood pressure data will be analyzed by special computer methods in the light of an extensive data base. (Longer series of readings are possible as well, and you may be told that more monitoring is needed because 7 days were not enough, for instance if you are hypertensive and your physician changes your medication.) monitoring records, as compared to conventional ones, allow a less inaccurate evaluation of high-risk patterns of blood pressure and heart rate than do conventional approaches. For example, there could be an unacceptable degree of change within a day, as well as unusual times each day when blood pressures are high and/or low. A larger-than-usual change in blood pressure, called CHAT (circadian hyper-amplitude-tension) usually precedes an overall elevation in blood pressure and is an indication or predictor of a great risk of diseases. The data bank at the University of Minnesota has the reference values for the thresholds at which, for a given gender or age, for Asians or whites, the variability of blood pressure is too high or that of heart rate too low. If you are of different ethnicity, the data base from whites will be used until the data base has been extended to your background.

Among other abnormalities, a blood pressure pattern peaking at odd hours also warrants further examination. The detection of unusual patterns in blood pressure change during a day or week can prompt a quicker follow-up and earlier preventive treatment, when needed.

Moreover, a blood pressure increase is more reliably evaluated with regard to when it occurs. And it can be more meaningfully treated in the light of information provided by expert analyses.

Rationale for offering chronobiologic blood pressure and heart rate monitoring and analysis

Benefits to residents

Blood pressure monitoring on a 24/7 basis—according to chronobiology—can provide you with a number of benefits that a traditional blood pressure reading cannot:

- It gives you early warning signs of a heightened cardiovascular disease risk, which can prompt preventive action.
- It improves on the traditional diagnosis of acceptable vs. abnormal blood pressure.
- It helps you and your physician in making the decision to address your blood pressure problems.
- It can help your physician in the selection of the most appropriate treatment and dosages, if drug therapy is recommended.
- It provides a better assessment and validation of the treatment you receive, particularly when treatment results in an increase of the extent of daily changes in blood pressure.

When you get an erroneous diagnosis as a result of the traditional method, undesirable consequences can occur:

- If you're diagnosed with high blood pressure but do not have it, you may experience occupational discrimination or a difficulty in obtaining health insurance. Treatment with drugs may be accompanied by side effects, such as impotence, cardiac arrhythmia or cough. Drug therapy may strain your finances.
- If you're incorrectly diagnosed as having normal blood pressure—when, in fact, you have high or otherwise abnormal blood pressure—the risk of stroke, kidney and heart disease increases, and with it the probability of organ damage. Minor symptoms such as easy fatigue and headache can gradually appear that may unnoticeably impair your performance. Worst of all, painful and costly debilitating illness or death may occur, perhaps in 5% of the population with an altered variability pattern such as CHAT.

Why chronobiologic monitoring and analysis?

Chronobiologic monitoring and analysis can identify, under

routine conditions, persons at risk of developing a high blood pressure or heart disease by assessing the daily pattern of change in blood pressure and heart rate. Several international meetings, including a special session of a National Academy of Medical Sciences, have reviewed the evidence and have endorsed the following points:

- Chronobiologic monitoring provides a more refined diagnosis of abnormal blood pressure by focusing not only on changes in the average, but also on altered daily patterns of blood pressure change. This approach may mostly benefit persons with borderline or unstable hypertension, assumed by others on the basis of spotchecks carried out on many patients to represent a large majority of the population with abnormal blood pressure.
- It should reduce the consequences of false positives and the misfortunes associated with false negatives, such as catastrophic diseases.
- It provides improved reference limits specified in time and derived from extensive data on healthy individuals.
- It allows physicians to determine the duration, extent and timing of elevation in blood pressure or heart rate to gauge potential organ damage, as documented for the case of the weight of the left chamber of the heart as endpoint.
- It may help your physician decide whether to recommend drug or non-drug therapy (such as changing your consumption of salt and caloric intake, exercise or self-hypnosis). And it helps to determine the timing of your treatment.
- After treatment's been initiated, this diagnostic technique helps to establish an individual's response to treatment, if the 7-day or longer monitoring is repeated.
- And it can continue to monitor the success of therapy by a control chart so that prompt action can be taken when problems arise.

Recommendation for the Diagnosis of Abnormal Blood Pressure

The chronobiologic method of blood pressure diagnosis—which consists of systematic 7-day (and, if need be, longer) monitoring of every individual's blood pressure in all age groups and with or without disease of any kind—works best when an ambulatory monitor that is programmed to automatically inflate the cuff at intervals is used, such as the monitor the city of Roseville is placing at your disposal. Moreover, the diagnosis by chronobiologic analyses—based upon the comparison of a given individual's data at a given time, with data obtained earlier on the same individual and/or with a large store of reference data from healthy peers—can pick up abnormality not otherwise detectable. When such abnormalities are found, there can be a 8.2-fold increase in the risk of stroke and a great likelihood of benefit since effective therapy has been found for this condition of an altered variability pattern [40].

Conclusion

Spontaneously, Michael Fossel, editor of the Journal of Anti-Aging Medicine, has written [40]:

> – 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.

All analogies serve only as hints, but hard data are available [35–47]. The foregoing analogy is used to indicate simply that blood pressure and the underlying stroke volume and compliance of the vessels are rhythmic and hence should be assessed by more than spotchecks. In this sense, a Citywide Blood Pressure Monitoring Project can be a first step toward flying through the mountain range of blood pressure and heart rate variation patterns with open eyes. In so doing, we can learn about the prevalence of altered blood pressure patterns and the incidence of events associated with such altered patterns in our own back yard. Some may regard this aim as utopian, or at least as hyperbole. Scrubbing before surgery and antisepsis broadly were once ridiculed. There is nothing ridiculous in the fact that leaders in hypertension-medicine who were hypertensive have self-measured themselves for a lifetime several times each day, with analyses by desk computer [48, 49]. It is so much easier and more efficient today. The health watch aims as a first step not only at clean and safe streets and clean air, but also at as clean and as safe a circulation of blood as one can make it by self-help with education and instrumentation available as a public service, with as few "accidents", such as strokes, heart attacks and kidney disease, as thus possible.

Epilogue

Taking *the* blood pressure in an emergency is a must, or at least taking *the* pulse; but by 1904, Janeway advocated that routinely multiple measurements should be taken before a patient is seen by the physician. This is now feasible and practical with the new hardware and software as well as with the reference values. The merits of scrubbing before surgery were once questioned but are universally recognized as essential today for preventing the spread of infection. Teaching children to read and write was once reserved only to a few privileged citizens, but is now available to everybody.

Monitoring of blood pressure and heart rate may also soon become routine once it is realized that, at a cost of Australian $60 million, a trial for mild hypertension showed that 48% of the "mild hypertensives" who entered the study and received a placebo ("sugar" pill) were "cured" after three years of such "treatment." Systematic measurements taken while following one's daily routine, analyzed chronobiologically, may detect what the naked eye cannot see in "good values." There are, of course, responders to placebo. But there are also an undetermined number of false positive and false negative diagnoses at the entry and at the end of such studies. The chronobiologic approach may lead to the correct diagnosis and may help physicians select the appropriate treatment. The Citywide Blood Pressure Monitoring Project can be a step in that direction.

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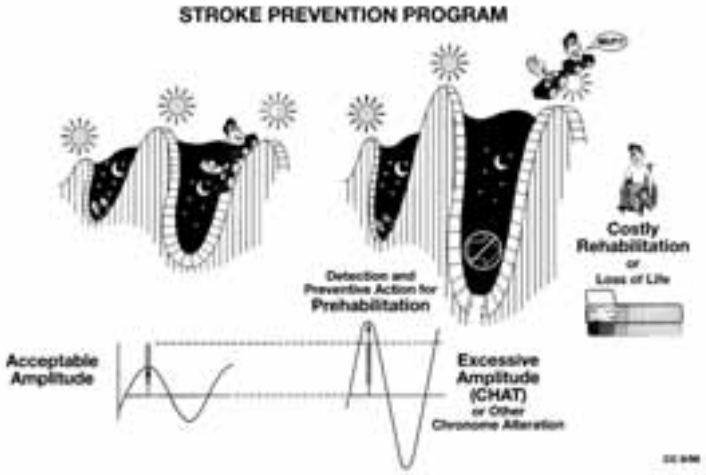

Graphic illustration of Editor's Note (40) conveying the desirability of assessing dynamic characteristics of change in blood pressure and in very many other variables. As a follow-up, the mayor of a city of about 34,000 wants to offer 7-day blood pressure and heart rate monitoring as a public service, comparable to safe streets and clean air and water. ©Halberg.

20th century scenario

Against this background, it may be understood why, a quarter-century ago, a keynote lecture at a Capri symposium, introducing the first drug (Dutimelan 8 15) which carried timing (8 a.m. and 3 p.m.) in its name, was entitled "Protection by timing treatment according to bodily rhythms: an analogy to protection by scrubbing before surgery" [50]. Superficially, scrubbing has nothing to do with chronobiology, except perhaps that the need for antisepsis, like that for acting, according to an interwoven time structure of rhythms, chaotic changes and trends (the chronome of each variable) was extremely slow to be recognized.

The present generation of patients and their physicians is benefitting 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 currently 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 asepsis and antisepsis to be accepted. Many amputations had to be done 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 this chronobiologic scenario, even in the university where this science reportedly originated [51].

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 greeted the speaker as an apparent friend and assured our delegation of prompt action. His assistant commissioner, John Harter, appraised us that once the commissioner was alone with his staff, however, he decreed "business as usual," unaware that John, who had introduced alternate-day treatment with corticoids, was a chronobiologist *par excellence*! It was disappointing to learn of the actual failure of a seemingly successful mission.

Admonitions to take chronobiology into account and to exploit it much more often fall on deaf ears. Both the merit of antisepsis and of chronobiology were presented at prestigious meetings, including academies of medicine. Proponents of chronobiology have become academics. Nonetheless, this new discipline is taking a very long time to penetrate actual medical 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 and did not live to see the full acceptance of antisepsis[2].

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.* 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 1933, Arthur 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 Societies of Internal Medicine and Endocrinology, confronted with the suggestion to treat at meal times, referred to "this idiocy of *three times a day"* [52]. The merits of compliance by drug use at meal times notwithstanding, Gross in 1985 again preferred a time-targeted treatment [53]. 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. 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.

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. 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. On the basis of a statistically significant alteration, warnings can be found and given for timely intervention whenever deviations from chronobiologic dynamic norms occur.

Acknowledgments

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Footnotes

[1] **An original seminar** included in this paper was dedicated to the memory of 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. Norberto was an internationally active advocate of a human chronome (time structure) initiative, which he recognized as an endeavor required in its own right, and also visualized the complementarity of the human genome and chronome initiatives. The chronome, as the phenotypical complement to the genome, adds to the latter a dimension of health; otherwise the genome initiative remains in its current homeostatic straitjacket of focusing mainly upon the multitude of genetic diseases and upon clocks rather than also upon a time structure much broader than biological time measurement.

We also remembered several outstanding late medical administrators, chronobiologists themselves, and all former associates in research and/or friends.

Frederic C. Bartter (of Bartter syndrome), Head of the Hypertension-Endocrine Branch and thereafter Clinical Director of the Clinical Center at the National Institutes of Health (NIH), Bethesda, Maryland, USA;

Howard Levine, Director of Medical Education at New Britain (Connecticut, USA) General Hospital and Professor of Medicine at the University of Connecticut in Farmington. Both Fred and Howard were MESOR-hypertensive and, from the time FH first had a chance to advise them, self-measured their blood pressure, not just for 7 days, as advocated only for people in apparent clinical health, but several times each day until the ends of their lives;

Florian Delbarre, Professor of Medicine and President of the Université Rene Descartes in Paris, France;

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 and later Dean of Nagoya State University and a councillor in Japan's parliament, the Diet.

Among the living, three administrators helped make possible the start of a human chronome endeavor at the Chronobiology Laboratories at the University of Minnesota:

Cherie Perlmutter, Acting Vice-President for the Health Sciences at the University of Minnesota during the span of the developments reported herein which underlie this position paper.

Duane Alexander, pediatrician and Director, National Institute for Child Health and Human Development, NIH, who, with Claude Lenfant, Director of the NIH's National Heart, Lung, and Blood Institute, overrode an insufficient score for an application evaluated by colleagues who presumably take *the* (casual) blood pressure; and

Joseph Rigatuso, Associate Clinical Professor of Pediatrics

at the University of Minnesota and Director of Research at Group Health Inc. (Minneapolis, Minnesota), with whom we have presented a case which typifies the suffering and cost associated with the benign neglect of chronobiology.

In the intervening years, we also lost Jürgen Aschoff, Agostino Carandente, Rudolf Engel, Erna Halberg, Gunther Hildebrandt, Chris Künkel, Heinz von Mayersbach, Werner Menzel, Boris Nikityuk and Colin Pittendrigh, Betty Sullivan (Fig. 3), and Brunetto Tarquini. The field reviewed herein owes all of them an indelible debt. Today's reductionist scientific climate can hardly afford to ignore their integrative contributions and in particular the fact that, as a function of timing, the same dose of the same molecule can inhibit or stimulate DNA synthesis [54]. We should know what time it is at all organization levels. On occasion, all of those named above must 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], I shall be enjoying in the hour of my death the conviction that sooner or later this time will unquestionably come."

[2] **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 him to coin "circadian" and eventually to the development of the new science, broader than biological time measurement, pertinent to any variable characterized by a ubiquitous circadian rhythm. 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 (by about half an hour) 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, apart from biological time measurement, he was at the threshold of resolving a terribly confusing, potentially ubiquitous source of variation. If one of two groups being compared free-runs and the other was 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 at a given fixed time of day. These changes in the sign of an intergroup difference are unpredictable unless the free-run is recognized and the period assessed objectively by inferential statistical methods. Hence, FH decided to scrutinize this finding further by continuing measurements around the clock for as many days or (as 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 many others as well as himself.

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 fo r four decades. A few years before these laboratories' director 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). In 1987, a report on "Focus" suggested that chronobiology space be reassigned to clerical accounting staff. It is hoped that the parallel with Semmelweis stops here.

Betty J. SULLIVAN, the first lady of cereal chemistry and mentor of the time structure, the chronome, found in every variable in and around us, died in Bloomington, Minnesota on December 25, 1999, at 23:30. She had been in touch with her environment intellectually, was fully functional and well-cared for by family members and long-time friends including librarian emerita Alice Wilcox. Notwithstanding a progressive multifactorial lung disease with components of airway obstruction, a probable pulmonary embolism, following a hip fracture and a coexisting valvular heart disease, she continued to place her state on the map of cereal chemistry and beyond.

Betty Sullivan was born in Minnesota on May 31, 1902. As a budding chemist, Betty's undergraduate work for a bachelor's degree in chemistry set her professional course, starting with a thesis based on the polymerization of a bicyclic terpene hydrocarbon, prinene, found in turpentine oils and used as a solvent. Upon graduation, she was the first woman to be employed as an assistant chemist at the Russell Miller Milling Company in Minneapolis. After two years of work, Betty pursued further education in biochemistry, receiving an international education scholarship from the University of Paris. She worked in the fermentation division of the Pasteur Institute, and also had the opportunity to learn from two-time Nobel laureate Marie Curie (1867-1934). After her return from Paris, as chief chemist at Russell Miller, Betty pursued further work in biochemistry, earning

her Ph.D degree with a thesis on the lipids of the wheat embryo. She became expert in the development and marketing of products which use grains and/or seeds as raw materials. The determination of moisture and the organic constituents of wheat and flour, and their relation to gluten quality, were all within her interests, as was the isolation of glutathione from wheat germ and its effect on the oxidation and reduction of flour. She became an authority on the chemistry of wheat proteins and the technology of baking.

In 1947, Betty became vice-president and director of research at the Russell Miller Milling Company, and when her firm merged with the Peavey Company in 1958, assumed the same position at Peavey, being responsible for development, market research and process engineering of new foods and chemical derivatives for proteins and sugars. When Betty reached the mandatory retirement age at Peavey of 65 years, she helped found a consulting firm, Experience, Incorporated, where she assembled corporate executives and retired university professors, consulting through the Agency for International Development and the World Bank for developing countries as well as for corporations in the field of U.S. agribusiness. Many more details are available in a biography written by Marilyn McKinley Parrish, who notes that Betty's greatest satisfaction came from discovering "something no one knew before, in my own case, the finding of the presence and identification of glutathione in wheat germ, and its effect on flour properties".

Erna Halberg, Franz's loving wife and former research associate in our laboratories, had worked with Betty and published in cereal chemistry. A lifelong friendship developed on this basis. Betty became a family member, and we learned of her many humane as well as scientific qualities by her ongoing critiques of the new discipline of chronobiology. Sometimes, she did not see where new pieces of the jigsaw puzzle fitted. She was supportive nonetheless, when she found that our interests had "changed" to something else, and eventually saw the broader chronome picture.

If we seek to draw a parallel with Marie Curie, Betty wrote extensively in a new field, as did Marie Curie. Betty and Mme. Curie lived in overlapping but greatly different times: While Mme. Curie declined to patent her processes or otherwise to profit from the commercial exploitation of radium, Betty held the patent on a flour improver, on accelerated moisture conditioning and milling of grain, and on a method of obtaining protein-rich flour. She did in her field what Alexander Graham Bell and Guglielmo Marconi did in theirs. De gustibus ...

Betty was an honorary member of Iota Sigma Pi, the society of women chemists. She was on the front cover of Chemical and Engineering News in 1948 (report of award in June 14 issue; cover story July 12) when she received the Thomas Burr Osborne Medal of the American Association of Cereal Chemists. In 1953 she was the recipient of the Outstanding Achievement Award from the University of Minnesota. In 1954 she was awarded the Garvan Medal of the American Chemical Society, and was again featured on the cover of Chemical and Engineering News (March 22). Among her many other professional distinctions, Betty was President of the American Society of Cereal Chemists in 1943-1944; chaired the Minnesota section of the American Chemical Society in 1950-1951, and served on the boards of the Journal of Agricultural and Food Chemistry, of Cereal Chemistry, and of Biological Abstracts.

With the undersigned, she participated in the demonstration that a calorie is differently handled at breakfast as it is at dinner. Although she did not accept co-authorship, Betty contributed substantially in design, analysis and critique as well as by arranging for the funding of this work. From 1988 through the end of 1999, Betty's generosity helped bring to fruition 976 published titles (and more still in preparation), many of which specifically acknowledge the support of the Dr. Betty Sullivan Fund. Betty was the center of attention when visitors from around the world learned from her, whatever their topic of specialization may have been. She commented on their work mostly in English, but was also fluent in French and understood German and Spanish.

Those like Betty who enable and foster the work of many and guide international developments, aiming for a better world with food for everyone as well as clothing, housing and health, are few and invaluable. Albeit they are scientists in their own right, they bat for much more than hard science. Betty Sullivan's sincere, deep interest and ever-willing helping hand touched on many topics. In particular, she advocated a budding chronobiology and chronomedicine, that splits and enters the range of everyday physiology, in which earliest disease risk elevation can be detected and acted upon before catastrophic disease occurs. One of her legacies is the chronobiology center at the University of Minnesota, which she helped to bring into being. Chronobiologists can only express gratitude which Betty, upon accepting the Osborne Medal, described as "the memory of the heart", wherein, far beyond being the board member of the Chronobiology Center, she was a friend and adviser to all. When Erna died in 1993, Betty wrote that "the world is a better place because of Erna". The same can be said of Betty. A laudatio in 1948 concluded: "What is going to happen to Betty Sullivan couldn't happen to a nicer (or a more worthy) person" (in the context of the Osborne Medal). The fifty-one intervening years by far extended this statement. As stated on the cover of Chemical and Engineering News on July 12, 1948, "She Analyzed the Wheat and Improved the Flour", and in the interim did much more in human relations as well as in science for a less hungry world.

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