

# HEALTH AND STRESS

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## WHY TIMING IS EVERYTHING: A CHAT WITH FRANZ HALBERG

KEYWORDS: William Best, Frederic Bartter, The Vanishing Physician-Scientist?, Linnaeus, "Halberg's paranoia" and circadian desynchronization, chronomes, Terukazu Kawasaki, dipping classification, treating hypertension by calcium and sodium supplementation, prehypertension, John Merrill, self-ambulatory monitoring.

Franz Halberg is best known for coining the term circadian (from the Latin *circa*, "around", and *diem* or *dies*, "day"), and is generally acknowledged to be the "Father" of chronobiology and chronotherapy. More to follow about the crucial but generally unappreciated significance of these concepts for practicing physicians, and especially cardiologists. However, I would like to begin this interview with Franz by discussing how he became interested in biological rhythms, which, apparently started in the early 1950s when he was involved in studying various effects of adrenal cortical hormones.

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Although invited to work in London with Sir Alexander Fleming, who had received the Nobel Prize for discovering penicillin, he accepted a WHO fellowship in 1948 to pursue his interest in endocrinology. His intention was to study under Fuller Albright, widely recognized as the consummate clinical endocrinologist of his era, who had attracted a stellar group of researchers at Harvard's Massachusetts General Hospital.

### **The Thorn Adrenaline Test And Counting Eosinophils in Boston and Minneapolis**

By the time he arrived in Boston, Albright was significantly incapacitated by Parkinson's disease and was not accepting any new Fellows. As a result, Franz transferred to Harvard's Peter Bent Brigham Hospital, where George W. Thorn was actively engaged in improving the diagnosis and treatment of Addison's disease. He had developed the Thorn test as a diagnostic tool for this disorder based on studies by his group and others reporting that adrenaline failed to cause the normal drop in blood eosinophil counts in

these and other patients with adrenal insufficiency due to deficient secretion of cortisone-like hormones from the adrenal cortex. Halberg was well aware of Selye's animal research, which had contributed to the Mayo Clinic's demonstration of the dramatic effects of cortisone in rheumatoid arthritis, and there was heightened interest in identifying other corticoid hormones or substances with similar effects. His assignment was to investigate this, but since known corticoids were not widely available, he injected mice with various compounds to evaluate possible corticoid activity based on their ability to cause a drop in eosinophil counts. It was a formidable undertaking fraught with numerous obstacles that had to be overcome. Eosinophils are so named because they take up the red dye eosin in humans, but this is not as apparent in mice and a new staining technique had to be developed. Determining accurate before and after differences, was also difficult since counts were affected by numerous external influences and differences in various mouse strains. More importantly, the following year Franz found that what appeared to be **time of day was a major factor, and could even result in opposite conclusions at different clock-hours** when comparing group results. This was obviously not what the Harvard group wanted to hear, since it cast serious doubt on the accuracy of the Thorn adrenaline test. It is important to emphasize that George Thorn was generally viewed as an intimidating and formidable figure whose opinions were gospel. I suspect this did not make you very popular with him or his Brigham staff.

FH: Rhythms -- enemies or friends -- to be eliminated or befriended? At Harvard I was given the task of testing cortisone-like effects. Because of the great variability, my experiments involved implanting a relatively very large dose of 2.8 mg (2800 mcg) of each substance to be assayed to see if, like a similar dose of cortisone, it would cause eosinophils to essentially disappear in 4-6 hours, and to assure that this effect persisted for 24 hours. It was an example of fighting rhythms as enemies by trying to eliminate them rather than using them as markers or endpoints. I eventually realized not only that eosinophil counts varied during the day, but also that one could use certain stages of this reproducible variation for timing an assay. I learned that cortisone's ability to cause a drop in eosinophils also varied at different hours. I didn't learn how important this was until I went to Minnesota the next year, and demonstrated that **administering 1 mcg of cortisone at the right time could substitute for an effect on eosinophils based on 2800 mcg at any time**, a strong argument to account for 24-hour rhythms as friends to be assessed, rather than as enemies that can be "eliminated" only transiently.

Dalton and Selye's earlier studies on stress-induced eosinopenia covered more than 24 hours, but presumably, judging from their graphs with gaps, did not cover a human sleep span, the equivalent of their rats' wakefulness and activity span. Had they stayed up and used concomitant controls, they might very well have become chronobiologists a decade before my investigations by finding that a recurrent eosinopenia occurred spontaneously in the absence of imposed stress as well as in its presence. Then, and often now, the beginning of a study was labeled baseline or "zero time" on the abscissa,

implying that it constituted a sufficient precaution to dispense with controls, without any reference to the clock hour and synchronizing routines such as a lighting regimen or daily routine. This led to the very transient acceptance of the Thorn adrenaline test as a gauge of cortical adrenal function by several opinion-leading groups of investigators. In contrast to them, however, **I had found eosinopenia following injection of adrenaline in animals after removing all possible corticoid-producing tissue.**

In humans, it was up to William R. Best in Chicago, with over 700 cases studied, to soon demonstrate the uselessness of the Thorn adrenaline test in clinical practice, including studies on adrenalectomized patients maintained on small doses of cortisone. By coincidence, Best later started and, for well over 3 decades, has continued his invaluable series of data collection on himself, based on which our analyses provide insights into the many biospheric associations of helio-interplanetary and geomagnetism, a topic that is pertinent to your interest in bioelectromagnetic energies and your scholarly contributions to this emerging discipline in *Bioelectromagnetic Medicine*. I agree with your description of George Thorn, whose authority was rarely questioned. I had little direct contact with him as our lab was in Building D across Shattuck Street from the hospital, where he reigned supreme as Physician-in-Chief, as well as Hersey Professor of the Theory and Practice of Physick at Harvard, the oldest chair of medicine in the U.S. He was, however, aware of my findings, which at the time were dismissed as artifacts or deemed not important enough to discredit prior studies. Thorn's epinephrine test was discredited by much more extensive evidence published by Best (*nomen et omen* - "The name is fitting") soon after I left Harvard.

My one-year fellowship at Harvard was not renewed and I had an opportunity to continue in Minnesota (rather than using my return ticket to Austria, provided by Uncle Sam, who brought me over on the liberty ship SS Ernie Pyle). One of my most vivid memories is George Thorn's parting remark that he admired my "sticking to my guns", but that so many could not be wrong while I was right. The highlights of my days in Boston were visits to our mutual friend Fred Bartter at Massachusetts General Hospital, where he was one of the brightest stars in Fuller Albright's firmament. We later developed a very close relationship and collaborated on numerous projects and papers, since he had developed a keen interest in chronobiology, particularly with respect to the treatment of hypertension. Fred had hypertension, and gave me the opportunity of consulting at NIH, including his own blood pressure management, and along with others in his group, notably Dr. Hans-Georg Gullner, we designed and implemented a study demonstrating the circadian stage-dependent effects of prazosin, a sympatholytic hypotensive drug. Blood pressures were measured automatically every 30 minutes in 10 patients on the metabolic ward, who were recumbent and kept on a constant diet to reduce the effects of posture and physical activity. Every patient received a capsule, either 1 mg prazosin or an identical placebo daily, with the time of administration delayed by 4 hours every day. We could then conclude in 1979 in *The Lancet* that "... **effect and duration of antihypertensive drugs' action depend not only on dosage but also on the time of administration**". We subsequently learned that antihypertensive strategy must also consider the kind of drug as a function of the rhythm's characteristic alteration, and even the possibility of doing harm (apart from any

hypotensive effect) by trading a lowered blood pressure for the greater risk of an excessive circadian amplitude (at least in Japanese and Taiwanese).

PJR: Your trials and tribulations at the Brigham remind me of Seneca's "*Non quia difficilia sunt non audemus, sed quia non audemus, difficilia sunt.*" (It is not because things are difficult that we do not dare, but because we do not dare, things are difficult.) I met Fred Bartter during my short stay at the Brigham a year or so after you left, but did not get to know him until I was at Hopkins and later Walter Reed. My doubles tennis partner at Hopkins was John Eager Howard, a very close friend and colleague of Fuller Albright, who confirmed that Fred's relationship to Albright was that of a "gifted son", and he was Fuller's favorite, even though their personalities were quite different. It was evident that Bartter was brilliant, but he would always be number two in Fuller's shadow, so it was no surprise that he accepted a position at NIH, and eventually became Director of the Endocrine-Hypertension Branch of the National Heart, Lung, and Blood Institute, and later director of the Clinical Center at the NIH. While he is best known for describing Bartter's Syndrome (profound hypokalemia due to increased excretion of potassium, and normal blood pressure despite elevated plasma renin and aldosterone levels), he was a true Renaissance figure with numerous interests.

John E. Howard told me that Freddy studied mathematics and philosophy, had a vast knowledge of English literature, and was fond of quoting from memory lengthy sections of poetry, and especially Shakespeare. He played the violin, was a good singer and it was not uncommon for his family to rise and sing for guests. He had developed an early interest in wild mushrooms and eventually classified over 200 species. He became an expert in the diagnosis and treatment of mushroom poisoning, which can be lethal due to liver failure, and frequently lectured on this. He rarely worked alone, and with Burton Berkson and other NIH associates, introduced alpha-lipoic acid for the treatment of mushroom poisoning. Bartter and Berkson were appointed by the FDA as principal investigators for this drug and administered it to 79 patients with acute and severe liver failure at various U.S. medical centers, with complete recovery in 75. Fred once told me that he knew of 267 patients that had been saved from life threatening liver failure, and I believe this is still the only FDA approved treatment for amanita mushroom poisoning. Berkson later used it successfully in patients with viral and autoimmune hepatitis as well as chronic liver disease, and wrote a book about its other antioxidant benefits.

Fred lived in what many consider the "golden days" of American medicine, when we had physicians who were heroes, as opposed to today's celebrities. I was reminded of this by *The Vanishing Physician-Scientist?*, a recent book edited by Andrew Schafer, Chair of the Department of Medicine at Weill

Cornell Medical College and Physician-in-Chief at New York Presbyterian Hospital-Weill Cornell Medical Center, with contributions from over twenty leading authorities from other medical schools. This timely book bemoans the fact that there are now much fewer physicians like Fred, with the facility to go back and forth from the laboratory bench to the bedside and make meaningful contributions, and offers some solutions to this disturbing trend. I know that you and Fred had a long and close personal and professional relationship that led to his recording his blood pressure several times every day for the rest of his life. Based on this, he published a 1976 paper with several co-authors, including you, entitled "Chronobiology in the diagnosis and treatment of mesor-hypertension". He wrote about a patient who was seen by two different doctors and was diagnosed by one as normotensive, and another as hypertensive, because his blood pressure had been taken at different times. He also was a strong advocate of the cosinor method for evaluating blood pressure changes, which incorporates MESOR, amplitude and acrophase parameters and later used this approach to show that less than one in four hypertensives were salt sensitive. It would be helpful if you could explain what terms like chronobiology, MESOR hypertension, cosinor and acrophase mean, since they will be foreign and confusing to most of our readers. I recognize that this is a difficult assignment, and perhaps the best way to begin might be for you to tell us about your collaboration with Fred, and what prompted you to coin the term circadian. This is the more important since 24-hour rhythms had long been recognized in plants. In 1751, the Swedish botanist Linnaeus had actually designed a floral clock by arranging different species of flowering plant in a circular pattern so that the time of day was indicated by which one opened at a given hour. For example, in the daisy family, he used the hawk's beard plant that opened its flowers at 6:30 AM, and the hawkbit, which did not open its flowers until 7 AM. Furthermore, de Candolle had found non-24-hour rhythms in plants. I suspect, however, that you looked for phase-shifted and desynchronized circadian biological rhythms in mice, and then in humans, and perhaps you could comment on this and your hypertension studies with Fred Bartter.

### **Circadian Rhythms, MESOR Hypertension, Chronobiology & Chronotherapy**

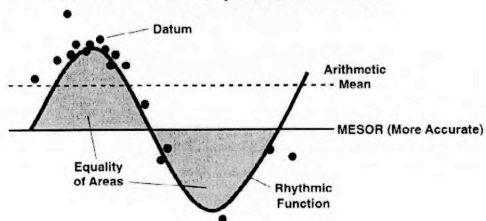
FH: In Minnesota, I was given the task of comparing two groups of mice, one with a very high incidence of breast cancer, the other with a very low incidence, the latter in association with a diet reduced in calories and the removal of the ovaries. The eosinophil counts differed with very high statistical significance. In order to replicate that study some days later, I got up earlier, compared the two groups again, and found no difference. For a third study, I got up still earlier; I found an opposite inter-group difference, but by that time I realized that the two groups differed in phase, and decided to count the eosinophil cells on the same animals repeatedly at intervals of a few hours rather than days. The inter-group difference in the rhythms' timing came to the fore and changed sign, revealing the phase difference as responsible for the differing results at

various times. The calorie-restricted mice received their freshly made-up diet in the morning and consumed it promptly; the control mice ate during the nocturnal dark span.

One puzzle was solved, but there was another in that differences in eosinophil counts between mice with and without eyes sometimes showed the anticipated day-night difference in animals without eyes, and sometimes the opposite difference or, again, no difference, while controls did what they were expected to do. Puzzle 2 was solved by years of 4-hourly around-the-clock rectal temperature measurements which, their variability notwithstanding, exhibited a desynchronized rhythm with a period differing from precisely 1 day, which a dear friend, Earl E. Bakken, responsible for the implantable cardiac pacemaker, described by analogy to a free-running oscillator. At that time, however, not everybody was complimentary. I dubbed Bakken's free-running "circadian desynchronization": my well-meaning department head called it "Halberg's paranoia". We attributed these findings of phase and frequency differences to the adrenal cortex as a clock; these were the basis of what became chronobiology. It became clear that in the presence of large-amplitude rhythms, their neglect could lead to very great blunders. Chronobiology, the study of time structures in us under fixed as well as varying standardized conditions, notably of lighting, environmental temperature, and feeding, taught us that **the same 2,000 calories are utilized differently at breakfast, leading to body weight loss vs. a body weight gain at dinner**. Assessing averages over full cycles with other characteristics usually had many merits, notably when there were more measurements, e.g., of blood pressure, during waking than during sleep. This fact led us to coin the MESOR, a midline-estimating statistic of rhythm that can be more accurate and more precise than the arithmetic average, as illustrated in Figure 1 below.

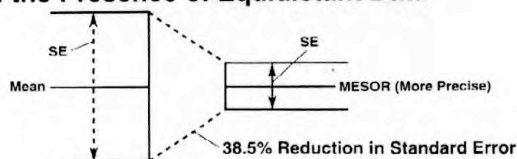
### ADVANTAGES OF THE MESOR OVER THE ARITHMETIC MEAN IN ESTIMATING LOCATION

Higher Accuracy (Smaller Bias) in the Presence of Unequidistant Data



The arithmetic mean does not represent true average for rhythm (defined, e.g., by cosine curve) when sampling is unequidistant and/or does not cover integral number of cycles.

### Higher Precision (Smaller Error) in the Presence of Equidistant Data



The SE of the mean depends on the total variability; a large portion of this variability can be ascribed to the rhythmic time structure; fitting an approximating cosine curve can reduce the residual variance, which determines how small the SEs of the MESOR and other parameters are. The better the cosine model fits the data, the greater the reduction in SE.

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Figure 1 - As can be seen to the left the MESOR shows greater accuracy and precision when compared to the arithmetic mean (notably in self-measurements that lack nightly values), and as seen to the right, greater precision than the arithmetic mean.

The term "MESOR-hypertension" indicates a MESOR of blood pressure above the upper 95% prediction limit of peers matched by gender and age. MESOR-hypertension is just one several vascular variability anomalies, VVAs (if abnormality is limited to a few days) or vascular variability disorders, VVDs, if abnormality is apparent in the fit of a 24-

hour cosine curve to replicated 7-day records as a whole, the 24/7 being a minimal sampling requirement at the outset. Other characteristics are measures of the extent of change and timing, the circadian amplitude and circadian acrophase, respectively. These novel endpoints can be altered in the absence of a change in the MESOR; these alterations can be detected by fitting cosines by least-squares and displaying them vectorially. Thus, cosine-fitting and display as vector led to the cosinor method, which is a microscope in time complementing the naked eye, notably when automatic measurements are made during sleep or activity. We recommended the cosinor in 1972 in *The Physiology Teacher* for schools; it can now be done automatically on computers. A vast literature rests on dipping classification predicting vascular disease risk. It ignores the fact that chronobiologic endpoints can work when dipping fails, e.g., in men or in prediabetes. Dipping may also mislead, as in Cugini's pre-hypertension. Indeed, dipping is simpler than chronobiology, if one follows Einstein's maxim that "Everything should be made as simple as possible, but not simpler." Dipping classifications become "simpler" in this somewhat derogatory sense when they fail under circumstances when the chronobiologic approach works.

Rhythms with a low frequency in limited data can show up as trends with again opposite inferences when their stages are ignored, as is the case for an about 9-year rhythm in the breakdown product of steroids, which almost certainly reflects solar activity. Apart from about 9-year rhythms that are also found in the solar wind, we find, in ourselves, many mirror images of the frequencies in the solar wind. When we measure blood pressure for decades as we have done, as has Dr. William Best (who measures not only blood pressure but also his body weight), a long-forgotten Brueckner-Egeson-Lockyer cycle is found. Since this is variable, we dubbed it "transtridecadal", defining it as a period, which is wobbly in its point estimate but covers the 30-40-year range with its 95% confidence interval.

In a set of nearly a dozen over 40-year series by Dr. Robert B. Sothorn of about 6 measurements/day, the principle of congruence, namely that of periods with similar length and with overlying or overlapping uncertainties became apparent, with 95% confidence intervals of the periods. This supports an association of his 1-minute estimation of mood, vigor and even systolic blood pressure, with some solar and other frequencies and with terrestrial magnetism, and at still other frequencies, with both. Moreover, these biospheric associations below the 1 percent level of statistical significance that have been demonstrated by us more than match the well-known relation of solar to earth magnetism with statistical significance. What may be of most interest to you is the recent association found between human mental functions on the one hand, and solar wind speed on the other. This is a step beyond chronobiology by recording rhythms in people for their time course in relation to rhythms in the environment near and far, while actually recording broader time structures of rhythms, chaos and trends, dubbed "chronomes". This endeavor led to another tool, the approach by chronomics to a transdisciplinary science that had its pioneers among Russian scientists, most notably Alexander Leonidovich Chizhevsky, who was offered a Nobel Prize but had to refuse it on Stalin's orders. But it took computers and satellites for us to ascertain in inferential statistical terms the associations of the human mind with



solar and terrestrial activity, as shown by odds ratios in Figure 2. (See Appendix) Incidentally, nonphotic associations are documented for infradian rhythms with sudden cardiac death and suicide and with diseases of society, crime and terrorism.

With respect to Fred Bartter, we met one evening at the Cosmos Club in Washington DC. He came with a young Japanese Fellow, Terukazu Kawasaki, and said "I have a gift for you: Teru". Terukazu Kawasaki did some sodium-related studies on a metabolic ward and Fred sent him to Minnesota with the data for analysis. We found, in strict, well-controlled studies at the NIH metabolic ward, as you, Paul, indicated that not all patients benefited from a reduction of sodium in the diet. In some, indeed, blood pressure decreased, but in others it didn't budge with statistical significance, and in still others it increased with statistical significance. Fred was not prepared to publish these cases. Our relationship cooled transiently, until one day he called and said "I had another case with an increase in blood pressure upon sodium deprivation". (I made sure that the case was published after Fred passed away.) Ludwig Poellman of the late Gunther Hildebrandt's group in Marburg, Germany, **had a patient he described as dependent on sodium to counteract his high blood pressure**. As it turned out, Kawasaki himself showed the different effects of sodium at different meals. Moreover, he proved to be the mainstay of a Kyushu/Minnesota study, perhaps the largest endocrine study in terms of number of hormones and density and length of sampling, in which we studied over 20 hormones around-the-clock in different menstrual stages in groups of women of different ages and along the seasons of the year. But this is another topic, perhaps for another day.

### **Rhythm Effects On Weight Gain, VVAs, VVDs And VVSs**

PJR: I highlighted some of your comments since they are so congruent with my own experience and interests. I was in charge of the Department of Metabolism at Walter Reed, and primarily involved in studies showing the effects of emotional stress on steroid secretion in monkeys at its Institute of Research. At the time, The Army became concerned that many officers were obese and obviously did not meet the weight requirements for entry into the Armed Services. In addition, since all had yearly physicals, it was evident that this had been a steadily increasing problem despite the fact that after each examination, they had been warned to exercise regularly and given a copy of a 1,000-calorie diet to follow. Many claimed that they had strictly adhered to these orders but continued to gain weight, even when they also took weight loss supplements. This was viewed with a great deal of skepticism, and ten severely corpulent senior officers with what appeared to be weight related cardiovascular and other problems were ordered to be hospitalized for a month at our Ward 38, where they could be carefully monitored, and no outside food could be brought in. They were all placed on 1,000-calorie diets, everything they took in and excreted was carefully measured. After 7-10 days on this regimen, it was clear that almost all failed to lose weight on this regimen and several had gained a pound or more.



During World War II, like many other of my high school classmates, summers were spent on a farm in Vermont participating in a program to replace young men who had been drafted. I recalled that although farmers usually ate a huge breakfast, I could not recall one who was obese, even if their duties did not involve heavy physical labor. I was reminded of the old adage "Eat breakfast like a king, lunch like a prince and dinner like a pauper." On a whim, I decided to substitute dinner for breakfast, and vice versa, and to everyone's surprise, most of our subjects lost weight on this same 1,000-calorie diet. By coincidence, an article in the current *International Journal of Obesity* reported that animals fed a high fat diet immediately after waking maintained their weight and had a normal metabolic profile. Those who ate the same meal at the end of the day gained weight and developed glucose intolerance and other manifestations of metabolic syndrome.

Several years later, when I entered private practice, my overweight patients, particularly females, also invariably complained, "I don't understand it doctor, I practically skip breakfast and hardly eat anything for lunch." Of course, it's not as simple as that and we now know that stress can cause the deposition of deep animal fat that leads to insulin resistance, diabetes, hypertension and other components of metabolic syndrome in animals and humans. In addition, stress influences the production of leptin, an appetite suppressing hormone secreted by fat cells. As I also noted in *DeStress Weigh Less*, stress causes some people to consume increased amounts of sweets and fast foods that pile on pounds. Our Walter Reed results were not published, but are described in more detail in this book, but I was not aware of your confirmatory study in mice and subsequent ones in humans that showed very different timing of cortisol vs. insulin and glucagon when people ate all their food for the day within one hour of awakening (breakfast-only) or not before 12 hours after awakening (dinner-only).

I have long protested the routine advice for all hypertensives to sharply curtail sodium intake, since this provides no benefits for the vast majority and can prove harmful. This ban has now been extended to the entire population regardless of age. New York City aims to reduce the sodium content of restaurant and packaged food by an average of 25 percent over the next five years, and there is now a resolution before the State Legislature to ban chefs and restaurants from adding any salt during the preparation of food as follows "No owner or operator of a restaurant in this state shall use salt in any form in the preparation of any food for consumption by customers of such restaurant, including food to be consumed on the premises of such restaurant or off of such premises." There would also be a \$1000.00 fine for "each use of salt." Two decades ago, Laragh et al demonstrated that low urinary sodium was associated with

greater risk of myocardial infarction in treated hypertensive men and subsequent studies have emphasized how dangerous sodium restriction and lowering blood pressure can be in the elderly. This mandates avoiding dairy products, a major source of calcium, which would be dangerous for a subset of **hypertensives whose elevated pressures fall when given calcium.**

Up until a few years ago, a blood pressure of 120/80 was considered normal and hypertension was not diagnosed unless it was consistently over 140/90. Due largely to the influence of pharmaceutical companies, 120/80 now puts you in a new category called "prehypertension" that requires treatment to prevent heart attacks, stroke or kidney disease. Contrast this to the chapter in Harrison's Textbook of Medicine decades ago, when there were few anti-hypertensive drugs, which stated "Whatever the form of therapy selected, it must not be forgotten that the physician who treats hypertension is treating the patient as a whole, rather than the separate manifestations of a disease. The first principle of the therapy of hypertension is the knowledge of when to treat and when not to treat. . . . **A woman who has tolerated her diastolic pressure of 120 for 10 years without symptoms or deterioration does not need immediate treatment for hypertension. Marked elevation of systolic pressure, with little or no rise in diastolic, does not constitute an indication for depressor therapy. This is particularly true in the elderly or arteriosclerotic patient, even though the diastolic pressure may also be moderately elevated.**" The author of this was John P. Merrill, a leading expert on hypertension, who was Director of the Cardiorenal section and laboratory at the Brigham during the time we spent there. Today, when we treat numbers rather than patients whose requirements differ, this sage advice would be grounds for malpractice.

I was therefore much heartened by a fairly recent article from your protégé, Terukazu Kawasaki and his colleagues, describing a Japanese woman with an extremely high blood pressure, first diagnosed when she was 38. Subsequent blood pressures ranged from 260/130 to 140/76, but no antihypertensive drugs were taken in the 25 years between age 56 and 80, when her regular doctor died. Her new physician prescribed several medications to lower her blood pressure, which caused such severe dizziness and fatigue that she was hospitalized at age 81. No remarkable cardiac, cerebral or other stigmata of hypertension were found despite blood pressures as high as 210/110, although this varied depending on when it was measured and by whom. After discharge, she was asked to record her own readings at home, which were always in an acceptable range. She died at age 95, but there was no evidence that this was from a CVA or other event related to her labile hypertension. As the authors concluded, "Although antihypertensive drug therapy may be helpful in some cases, it

may not be necessary in others. **Intensive drug therapy may even be harmful for misdiagnosed emotionally HT patients particularly those misdiagnosed with refractory hypertension, when the response to health care professionals may be emotional."**

I would value any comments on the above, as well as how chronotherapy can aid in treating hypertension, the value of self-ambulatory monitoring, and especially the recent flurry of interest in blood pressure variability.

FH: I remember John P. Merrill from the Brigham, and prior to submitting it for publication, Terukazu Kawasaki and Keiko Uezono kindly sent me the data on their patient, who reached the age of 95 despite a lengthy history of untreated hypertension. This illustrates Merrill's maxim that there are exceptions to every rule, as does recommending that everyone should sharply curtail sodium intake. As you emphasized, this mandate could have disastrous effects in certain hypertensives as well as normotensives, especially elderly individuals. With respect to your question about how chronobiology and chronotherapy can help practitioners treat hypertension, as you have also emphasized elsewhere, hypertension is not a diagnosis, it is only a description of a measurement higher than arbitrarily established standards that may not apply to everyone. The identical measurements could have varied causes that obviously require very different therapeutic approaches. A drug that is beneficial for one patient could be deleterious for another with the same blood pressure or even in the same individual if taken at different times of the day. I would go even further by arguing that "hypertension" is a misnomer, as I suggested in vain to some editors of journals with that word in their name. This was a somewhat quixotic endeavor embarked on when I was younger and more enthusiastic and idealistic. Fred Bartter would have supported this, as would you or any other objective observer who reviewed the wealth of data dealing with diverse aspects of blood pressure variability that are crucial to understanding the significance of transient elevations. It is my hope that at some future time, "hypertension" will be replaced by "alterations of vascular variability", which more accurately reflects the different etiologies and prognosis for the identical measurements.

Variability in this sense does not refer to differences recorded on successive spot check-based office visits, which is merely pseudo-evidence. Nor is the platinum standard 24-hour profile satisfactory, since day-to-day as well as week-to-week profiles are also unstable. To reiterate, there are VVAs (vascular variability anomalies) that last for only a few days, VVDs (vascular variability disorders) confirmed on consecutive 7-day around the clock records, and VVSs (vascular variability syndromes), consisting of combinations of VVDs. Abnormalities in any such diagnostic indicators of strain should signal the need for further surveillance. If treatment is indicated, the first step should be to identify causes and attempting to eliminate previously unrecognized or unvalidated influences by lifestyle changes before resorting to drugs. Other VVAs, VVDs and/or VVSs can also occur without evidence of a consistently elevated blood pressure or its MESOR (midline-estimating statistic of rhythm). Additional illustrations and examples of this are provided in Figure 3 (See Appendix).

The tensiometer on the wrist to which you allude must still be compensated for variability associated with position; it is not yet available, but is greatly needed. Examples are available for what physicians and patients can do by using routinely with chronobiologic analyses currently affordable devices that can be further greatly reduced in cost, as demonstrated by Larry A. Beaty of the Phoenix Study Group, composed of volunteering members of the Twin Cities chapter of the Institute of Electrical and Electronics Engineers (<http://www.phoenix.tc-ieee.org>)

As Michael Fossel, editor of the *Journal of Anti-Aging Medicine* (2), put it, with respect to what patients can do, nobody should fly blind when receiving hypotensive treatment. A popular drug such as Hyzaar, if prescribed without personalized surveillance, can induce a circadian overswing, i.e., a vascular variability disorder, VVD. A change in the time when the drug is taken can make the same dose of the same drug in the same patient beneficial or vice versa. To be specific, at one administration time, before noon (in the patient Su) Hyzaar induced the overswing of diastolic blood pressure and exacerbated it in the systolic. At another time of administration, Hyzaar eliminated a pre-existing overswing. These opposite effects were found in tests at 6 medication times, with the drug administered at each time for about a month, with half-hourly surveillance of blood pressure during the last week of each test span. These differences occur as a function of the timing of the drugs used at different best and worst times along the scale of 24 hours (among others, in studies by Dr. Yoshihiko Watanabe that we analyzed). Thus, the best time had to be found for the given patient. This optimization of treatment time, preferably when a newly diagnosed patient is placed on hypotensive treatment is an example of chronobiologically personalized health care that eventually may complement personalization by the individual's genome and is cost-effective itself today, while personalization by the genome is not so as yet.

Another example is a pregnant woman whose blood pressure overswing was reported to her obstetrician with suggestions for further monitoring and treatment. Our recommendation was ignored since the average of blood pressure over two days was below 120, a finding acceptable according to current guidelines, that as yet ignore VVDs. Pre-eclampsia ensued; the cost of her baby's care for 26 months was estimated to be 1 million U.S. \$, half of it cost-accounted. Both patient and caregiver may realize that blood pressure can vary a great deal, that high blood pressure is just one VVD, that its successful treatment can bring about a VVD associated with a bigger risk of ischemic stroke, and that accordingly before each routine physical examination a chronobiologically interpreted 7-day record of half-hourly around-the-clock measurements should be obtained to REPLACE the blood pressure measuring cuff currently in each physician's office.

Much of the current literature dealing with "white-coat hypertension" and "masked hypertension" recognizes only part of the problem. Indeed, blood pressure is characterized by a prominent circadian rhythm and responds in a predictable circadian stage-dependent manner to a wide range of stimuli, including the taking of a BP measurement in a physician's office. As a consequence, the same patient seen by two different physicians in the morning or evening can be diagnosed as normotensive by the

former and hypertensive by the latter. Physicians will eventually realize that treatment must not be allowed to depend on the time of day when a patient happens to be examined.

In summary: Better care at reduced cost is achieved by acting not only to lower an elevated BP but also by correcting other alterations in the variability of BP and heart rate (HR). These vascular variability disorders (VVD)s, including with a high BP, too large a circadian amplitude of BP, too large a pulse pressure, an odd timing of overall high values recurring each day in BP but not in HR, and too low a standard deviation in HR) have been associated with a large increase in cardiovascular disease risk in their own right and to increase that risk when they complicate an existing elevation in BP. By optimizing treatment (kind, dosage, and timing) to eliminate or reduce all VVDs as much as possible, it is possible to reduce the incidence of conditions such as strokes and heart attacks that are costly in terms of suffering as well as financially. Data from clinically healthy subjects serve to derive reference values, computed as time-specified 90% prediction limits along the 24-hour scale, further qualified by gender and age. Corresponding reference limits can likewise be obtained for the circadian characteristics, serving for the detection of abnormal variation in BP and/or HR. A small database in clinical health already available at the University of Minnesota Halberg Chronobiology Center is serving that purpose and demonstrated the feasibility of the proposed approach in several outcome studies.

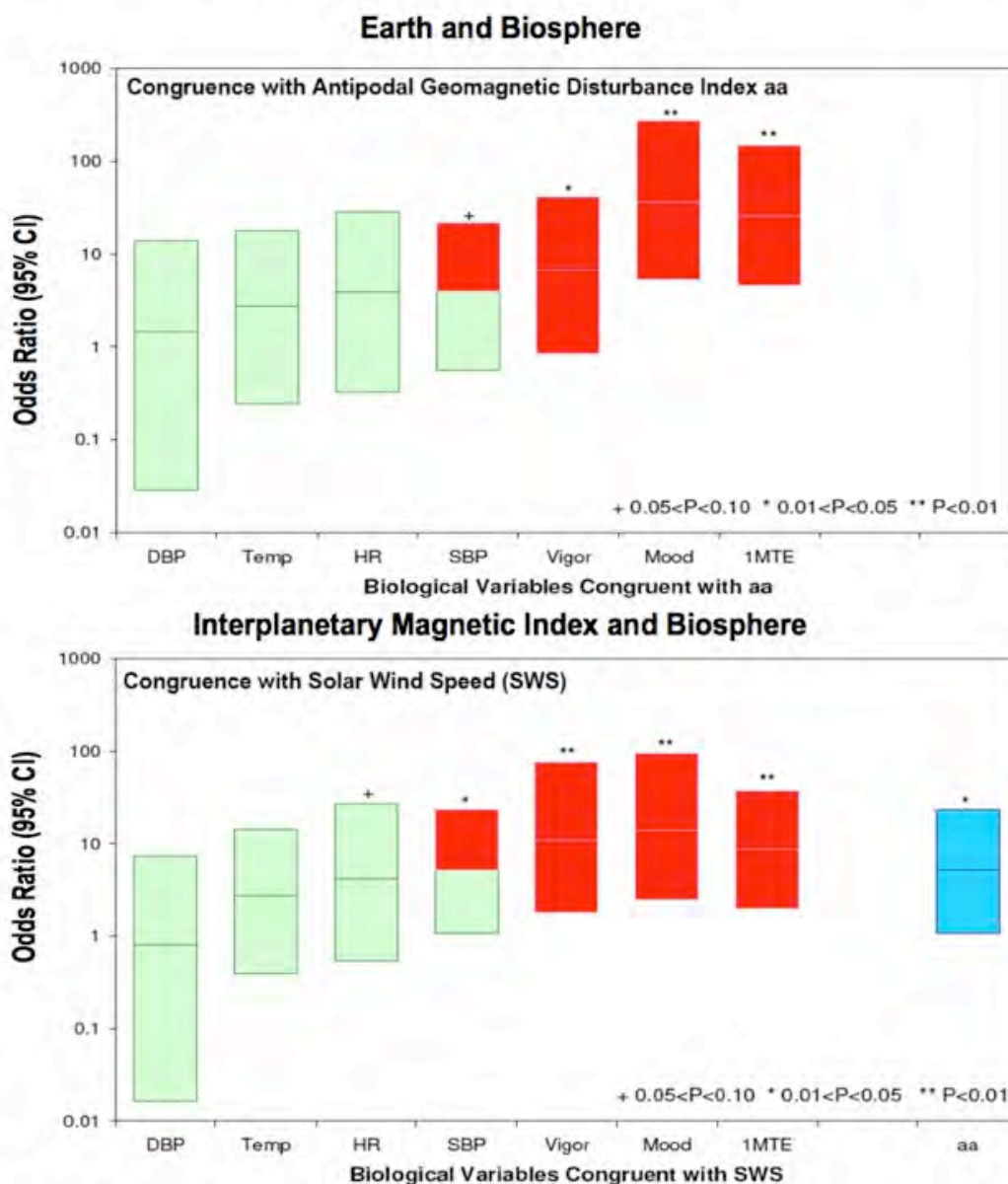
PJR: Due to space limitations, this brief review of your hypertension research could not include numerous references and additional diagrams. However, these will be available in an expanded version of this interview on our web site. A few of these can be seen in the Appendix that follows. Nor have we been able to discuss your extensive studies on solar and geomagnetic influences on health. I look forward to learning more about this and your other interests at the Third International Conference on Advanced Cardiac Sciences Conference in Saudi Arabia ([www.kingoforgans.com/english/main.php](http://www.kingoforgans.com/english/main.php)) We will devote a future Newsletter to this fascinating event — so stay tuned!

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Editor-in-Chief

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## Figure 2. Odds Ratios Of Associations Between Certain Human Mental Functions And Solar And Terrestrial Activity.

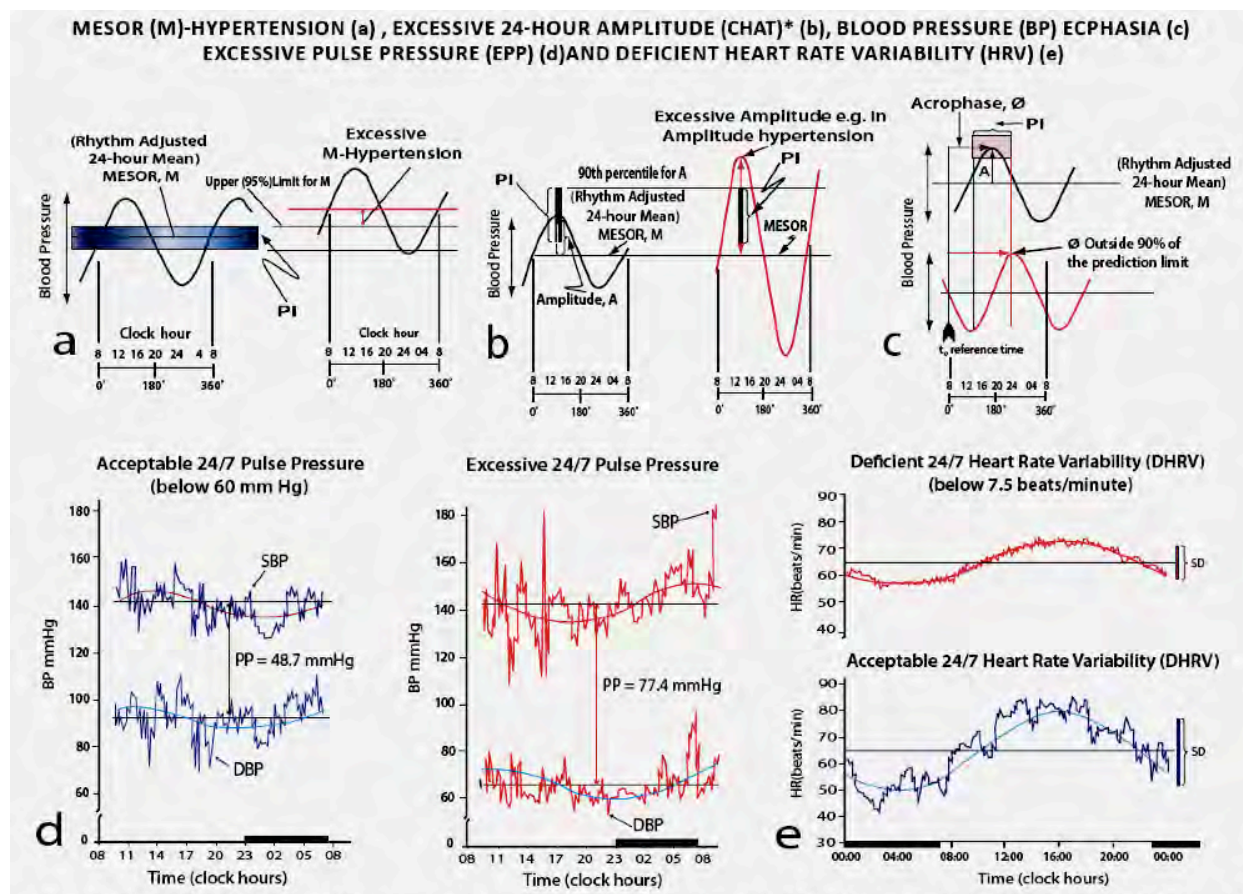
Human mental functions (vigor, mood and [1-minute] time estimation) are as closely associated with our cosmos, as is the well-known association of the sun's and the earth's magnetism (extreme lower right). Systolic blood pressure monitoring for preventive health maintenance provides data that, as a dividend, may serve to monitor the cosmos and its influence on societal diseases, crime and terrorism\*



\*By testing the likelihood that congruence (correspondence of common cycles in and around us) is due to chance.



**Figure 3** Definitions and illustrations of abstract vascular variability disorders, [a] to [c] diagnosed by cosinor (parametrically), [d] and [e] diagnosed by thresholds.



\* Above upper 95% prediction interval (PI) [for a and b], deviating from 90% PI [for c] clinically healthy persons matched by gender and age or above [d] or below [e] thresholds, all new standards requiring novel reference values from chronobiologically interpreted 24/7 records specified by gender, age, ethnicity and geography, from long distance disease-free dying at an advanced age.

### INTERPRETATION

[a] **MESOR-hypertension (MH)**, can be systolic (**S-MH**), diastolic (**D-MH**), mean arterial (**MAMH**), or a combination of these conditions, incomplete when demonstrated only parametrically (complete when complemented non-parametrically by an extent of excess during 24 hours > 50mmHg x hour).

[b] **Circadian Hyper-Amplitude-Tension (CHAT)**, which can also be systolic (**S-CHAT**), diastolic [**D-CHAT**], mean arterial (**MA-CHAT**) or a combination of these.

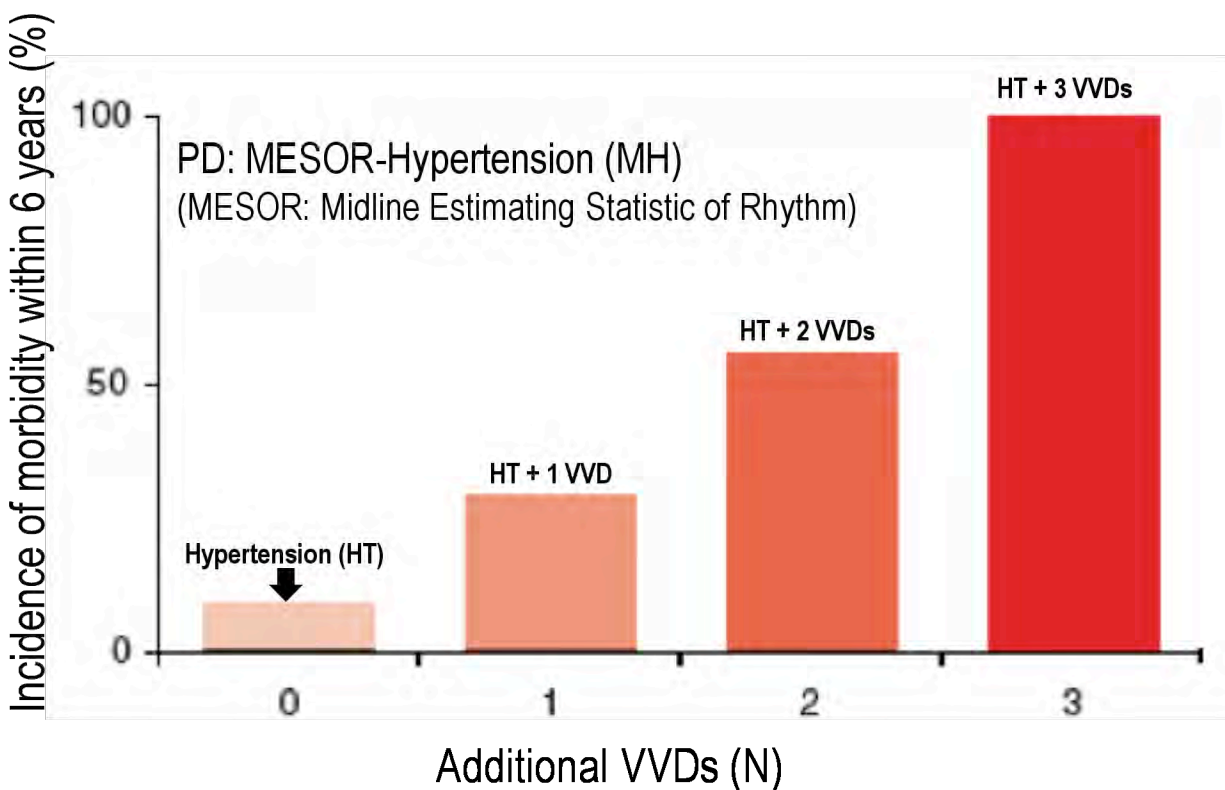
[c] **Odd timing of the circadian rhythm of BP** but not of that in HR (BP ecpasia).

[d] **Excessive pulse pressure (EPP)**, when the difference in the MESORs of SBP and DBP for adults exceeds 60 mmHg, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease-free long-life outcomes) specified further by gender, age, ethnicity and geography.

[e] **A deficient HR variability (DHRV)**, defined as a standard deviation of HR less than 7.5 beats/minute, a threshold that remains to be replaced by reference values from clinically healthy peers (eventually with disease-free long-life outcomes) specified further by gender, age, ethnicity and geography.



## Increase in Vascular Disease Risk Assessed by Actual Outcomes Within 6 Years of Monitoring in 297 Patients in the Presence of Multiple Vascular Variability Disorders (VVDs)

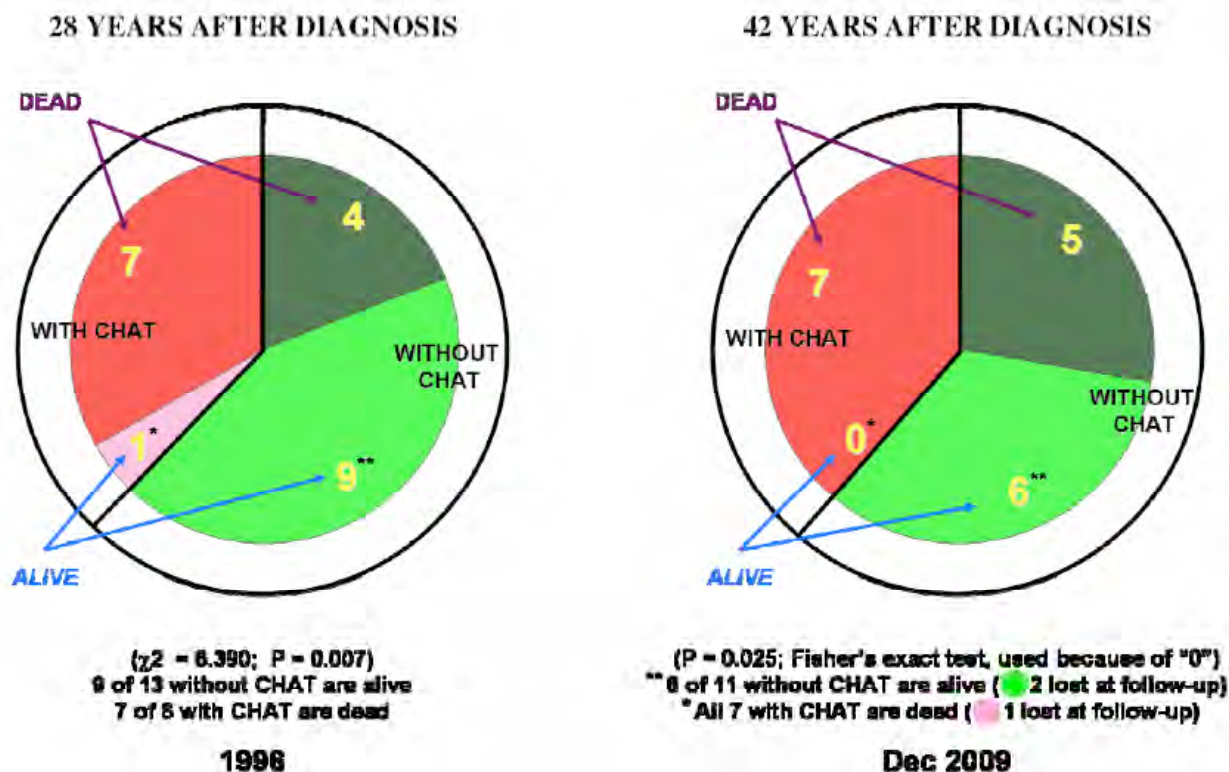


**The risk of ischemic stroke within 6 years increased from about 8.7% in hypertension alone, to 100% in the presence of added Vascular Variability Disorders (VVDs).**

Results stem from 297 patients, among which only 34.7% had uncomplicated hypertension and 40.7% were normotensive, including 2.4% and 1.7% with only CHAT or DHRV\*, respectively. For complementary results on 1,177 untreated patients. (see *Hypertension* 2007; 49: 237-239).

\*CHAT: Circadian Hyper-Amplitude-Tension, a blood pressure overswing; DHRV: Deficient Heart Rate Variability.

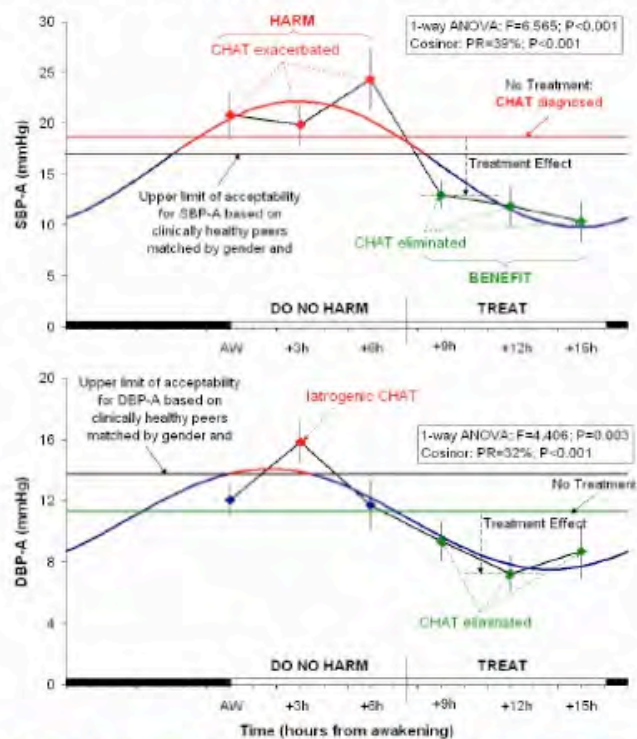
## ALL WITH A BLOOD PRESSURE OVERSWING (CHAT) ARE DEAD 42 YEARS AFTER DIAGNOSIS AS SEEN BELOW TO THE RIGHT



\*CHAT: Circadian Hyper-Amplitude-Tension. CHAT present vs. absent: red or pink vs. green; dead vs. alive: dark or light shading and violet vs. blue lettering and arrows. Original study based on manual blood pressure measurements by staff every 2 to 3 hours during waking for 2 days of 63 patients in Höhenried, Germany, with only partial outcome information.

An excessive prominence of the circadian blood pressure (BP) rhythm has been shown to increase cardiovascular disease risk. In this study, it is shown to be associated with a higher likelihood of overall mortality: at 28-year follow-up, only 1/8 subjects with this condition is still alive (12.5%), whereas 9/13 subjects with an acceptable circadian BP variation live (69.2%); of the remaining subjects not lost at follow-up after 42 years, 6/11 subjects with an acceptable circadian BP variation live (54.5%) but all 7 subjects with an excessively prominent circadian BP variation are dead (100%). Assessing BP variability by 24-hour/7-day monitoring at least once a year not only in special cases but in everyone is essential to detect abnormalities such as an excessive prominence of the circadian BP rhythm, so that timely interventions can be instituted to restore a healthy BP variability.

Treatment Beneficial at Certain Other Times (9, 12 or 15 hours after awakening) can EXACERBATE a Pre-existing CHAT in Systolic Blood Pressure (SBP) and INDUCE CHAT in Diastolic Blood Pressure (DBP) when Given at the Wrong Time in Patient Su \*

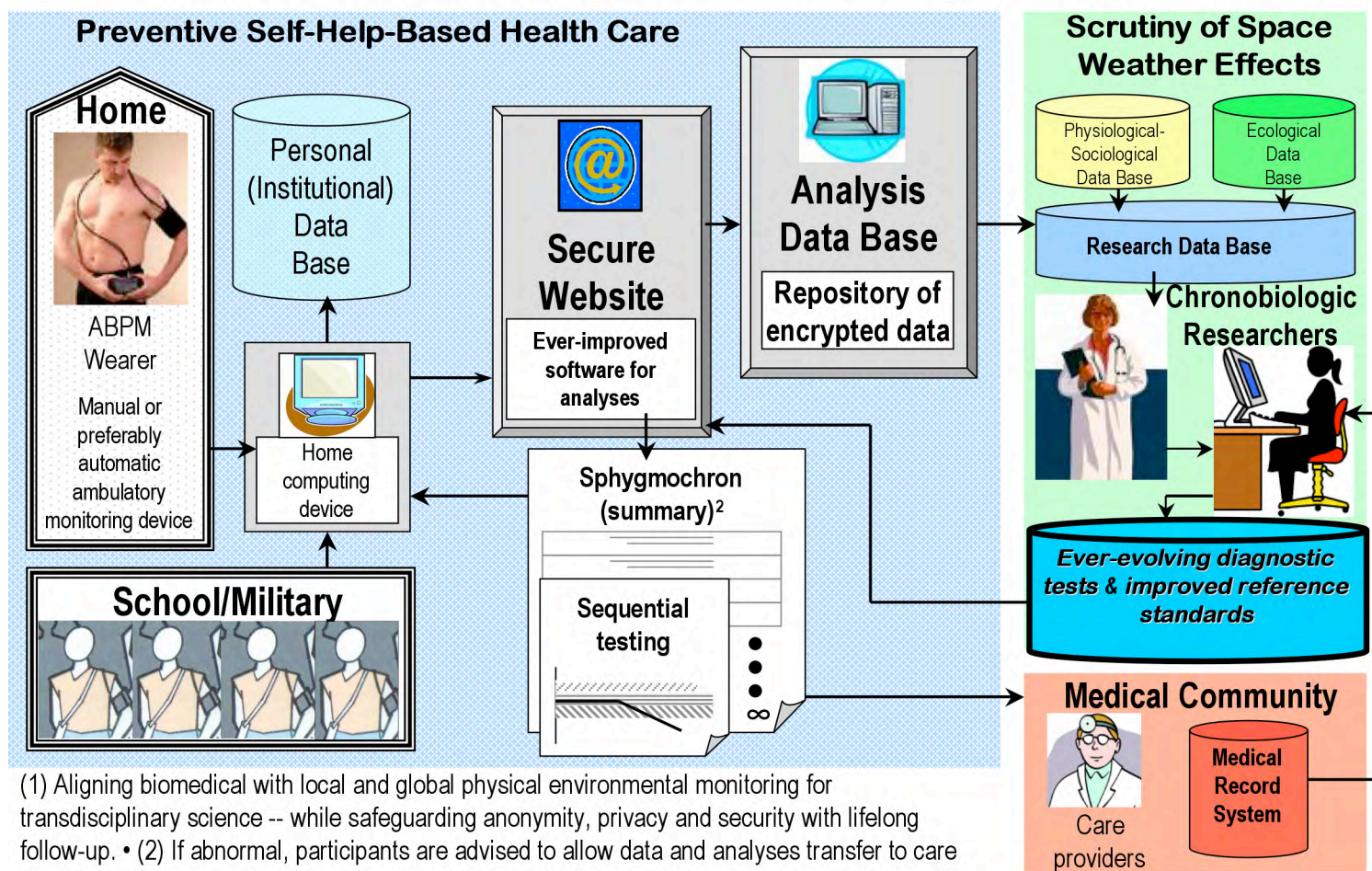


(Pieter Bruegel's 1568 *The Parable of the Blind Leading the Blind* is reproduced by kind permission of the Fototeca della Soprintendenza of the BAS PSAE and of the Polo Museale of the City of Naples.

\*Su., M, age 66, treated with Losartan (50 mg) and hydrochlorothiazide (12.5 mg). Each point represents the circadian amplitude of systolic (S, top) or diastolic (D, middle) blood pressure (BP) estimated from a weeklong record of half-hourly around-the-clock measurements after about one month of treatment at each of 6 different times (upon awakening, 3, 6, 9, 12, or 15 hours after awakening). In the absence of treatment, this patient has too large a circadian amplitude of SBP (CHAT, horizontal line above the upper limit of acceptability). Treatment for one month in the morning is associated with an increase in the circadian amplitude of SBP, thereby exacerbating the pre-existing condition (systolic CHAT). Treatment for another month at 3 hours after awakening is also associated with an increase in the circadian amplitude of DBP above the acceptable limit, thereby inducing diastolic CHAT. By contrast, treatment later in the day is associated with a decrease in the circadian amplitude of both SBP and DBP, eliminating a condition (CHAT) known to increase cardiovascular disease risk. It is important to assess the circadian rhythm in BP when prescribing anti-hypertensive medication, so that the decreased risk achieved by lowering an elevated BP is not hampered by bringing about an undue increase in the circadian amplitude of BP and thus the even higher risk that CHAT represents.



## Ambulatory blood pressure and heart rate monitoring of space weather



(1) Aligning biomedical with local and global physical environmental monitoring for transdisciplinary science -- while safeguarding anonymity, privacy and security with lifelong follow-up. • (2) If abnormal, participants are advised to allow data and analyses transfer to care providers for surveillance, diagnosis, optimization of treatment, if and as need be, and for ascertaining continued efficacy of treatment in the many millions of MESOR-hypertensives. Modified from Adams C. Int Conf on the Frontiers of Biomedical Science: Chronobiology, Chengdu, China, 2006, p. 64-69.

Visualization of a secure website that subjects can access to upload a 24-hour/7-day record of blood pressure and heart rate. Results from analyses are automatically returned to the subject. Only when abnormalities are found is there a need for the subject to seek medical advice. With given permission from the subject, the data can enter a database. In the absence of abnormalities and if confirmed by disease-free long-life, the data can enter the reference database to derive improved time-specified reference values and improved reference values for the circadian parameters and any other pertinent endpoint separately for men and women of several age groups. When abnormalities are detected, the data can be used to assess the efficacy of any intervention at a later date once data from repeated monitoring sessions are uploaded. Information about outcomes from subjects uploading data to the website is useful for research purposes aimed at finding other features associated with either potentially undesired or perhaps even beneficial effects. All data can serve to assess any effects on blood pressure and/or heart rate associated, among others, with weather in space as well as on earth.