RESOLUTION

FROM A
MEETING
OF THE

INTERNATIONAL SOCIETY FOR RESEARCH ON CIVILIZATION DISEASES AND THE ENVIRONMENT

NEW SIRMCE CONFEDERATION

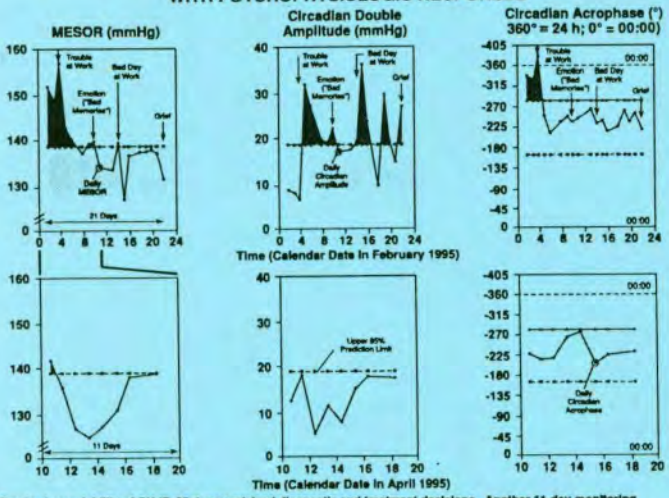
BRUSSELS, BELGIUM,
MARCH 17-18, 1995

Illustration of the problems to be addressed:

1. Diagnosis

How reliable and reproducible are casual blood pressure measurements and even results from 24-hour ambulatory monitoring?

INFRADIAN SYSTOLIC BLOOD PRESSURE (SBP) VARIABILITY ASSOCIATED WITH PSYCHOPHYSIOLOGIC RESPONSES*



* Day-to-day variability of CH (F, 60y) may mislead diagnostic and treatment decisions. Another 11-day monitoring in July 1995 found no blood pressure deviation.

MESOR-hypertension only for 5 consecutive days at beginning of record but not for ensuing 16 days (top left) or for 11-day span in April (bottom left) or for 11-day span in July (not shown). The circadian amplitude is acceptable for the first three days, but intermittently excessive thereafter in February (but not in April or July). Acrophase is deviant only initially.

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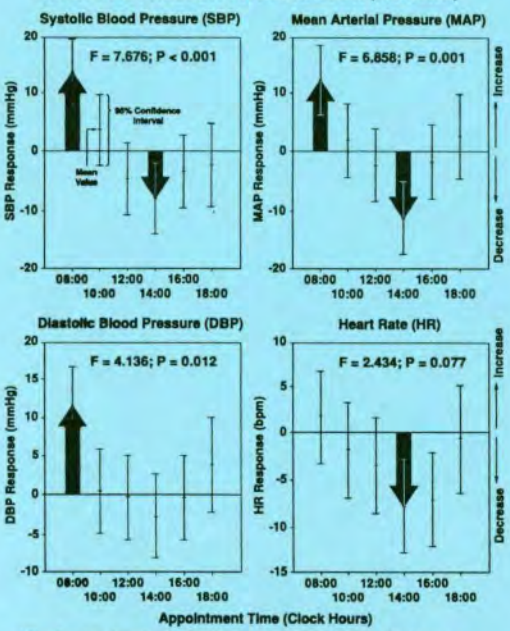
TIMING CLARIFIES AND QUANTIFIES TENSION ("STRESS") EFFECT AS PRESSOR OR DEPRESSOR (ARROWS)*



* Circadian-stage determines predictable increase or decrease of human blood pressure and heart rate during surgery; assessed as the difference, corrected for posture, between the mean value during the appointment and the value predicted from the circadian profile provided by each patient; results from ambulatory monitoring at 5- to 15-minute intervals for 3 days bracketing surgery on 23 patients (N = 254 sets of measurements per patient; total N = 5,840; including monitoring on two previous occasions: total N = 17,758).

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2. Intervention

Timing according to circadian stage can have drastically different effects and hence can be used to optimize intervention, including non-drug (p. 40) or drug (p. 41) treatment when needed. For instance, the same kind of surgery in the morning raises and in the afternoon lowers blood pressure and heart rate. Blood pressure can vary spontaneously from being too high to being acceptable, if not too low, during office hours. This resolution and evidence amplifying on it tell us what to do about it. It proposes the recycling of systematically collected, otherwise lost information and chronobiologic action on this basis with self-help (29, 30).

Fairy tale or reality?

Endeavors to interpret only values outside the normal range are Sisyphean to the point of recalling the tall tale of Baron Münchhausen's horse: the horse was cut in two by the town gate as it closed; when the head of the horse subsequently drank at the well, the water poured out of its severed middle onto the ground. Similarly, much information from within the physiologic range (the indispensable water in our analogy) is lost today, but may be usefully **recycled** tomorrow.

(Illustration by Martin and Ruth Koser-Michaels from Münchhausen: Des Freiherrn Wunderbare Reisen und Abenteuer, Droemersche Verlagsanstalt, Munich, © 1952, facing p. 32. Reproduced with permission of the publisher.)

Medtronic Chronobiology Seminar #8 · Presented by Franz Halberg and Germaine Cornélissen, University of Minnesota, Minneapolis, Minnesota 55455, and the International Womb-to-Tomb Chronome Initiative (3,4)

Resolution[1] on the utility of chronobiology[2] in clinical blood pressure assessment

The following chronobiologic rationale and approach are herewith agreed upon:

• Given that blood pressure disorders and their consequences are a major risk factor for vascular diseases that afflict a large portion of the population, lead to catastrophic, disabling diseases, and involve large medical costs (5);

• Given that in the case of a correctly diagnosed blood pressure disorder, anti-hypertensive agents are useful to reduce the incidence of adverse vascular events (5);

• Given that the current diagnosis of blood pressure disorders is associated with an error exceeding 40% as recorded in large clinical trials (involving thousands of participants), Figures 1 and 2 (6, 7; cf. also 8, 9) and has almost certainly obscured their outcomes (10) and given that an uncertainty of a similar extent is found in small chronobiologic studies, Figures 3 and 4 (11, 12);

• Given, therefore, that individuals are treated unnecessarily at great financial cost with side effects as well as the unwarranted stigma of a disease (13);

• Given that very busy medical opinion leaders3 (Figure 5a, 5b, 5c, 5d), among others of all ages (Figure 6), including centenarians (17) and children (Figures 6, 7; 18-24), have all taken their blood pressure by manual or automatic (7) measurements, some for spans of years, if not decades (25), and have thus documented the feasibility of self-measurements;

• Given that the teaching of chronobiology has been formulated as a concept and experimentally validated in elementary and middle schools as well as in colleges in North America (18-22) and Europe (23, 24);

• Given that the U.S. National Science Teachers Association has produced a book in support of chronobiologic literacy (26) and that a lead article on the topic was also published by the American Physiological Society (27) and by educators elsewhere (28);

• Given that a 24-hour automatically monitored blood pressure profile, summarized by more than daytime, nighttime and 24-hour averages, can detect deviations, including elevations at odd times when they are not likely to be checked by health care professionals (29, 30), Figure 8;

• Given that a chronobiologic analysis of blood pressure data collected around the clock resolves and quantifies endpoints such as an excessive circadian blood pressure amplitude, Scheme 1 (7, 31, 32);

• Given that an excessive circadian blood pressure amplitude is a risk factor for ischemic stroke and nephropathy at all systolic blood pressure MESORs, even below 130 mm Hg (Figure 9), and that it is a larger risk factor than any of the known risk factors for these diagnoses tested so far, Figures 10 and 11 (33, 34);

• Given that those patients with an excessive circadian blood pressure amplitude who by happenstance are examined when their pressures are low are misdiagnosed as normotensive and hence are left untreated despite their much increased risk of developing an adverse vascular event;

• Given that those other patients with an excessive circadian blood pressure amplitude who by happenstance are examined when their pressures are high are likely to be treated with antihypertensive drugs aimed (for the sake of compliance) at 24-hour coverage, although the further lowering of their blood pressure when it is naturally low may not be warranted and may in some cases even be harmful (7);

• Given that the treatment of blood pressure disorders timed according to biologic rhythms (e.g., circadian stage) (chronotherapy) achieves more of a hypotensive effect sooner with a lesser dose and fewer complications as compared to traditional treatment for the case of propranolol, clonidine and a-methyldopa (Figure 12; 35, 36; cf. also 3), among others (37);

• Given that an automatic blood pressure monitoring profile limited to 24 hours, even when it is analyzed for chronobiologic endpoints, can yield drastically different results for the same patient studied on different days, Figures 13-15 and Table 1 (38);

• Given that control charts can assess the success or failure of a given treatment so that the required effect, Figure 16, or the lack of such an effect are ascertained on an individualized basis (39);

• Given that the use of such control charts can be rendered practical in terms of sampling requirements, Figure 17 (39), as can be sampling by self-help for screening and diagnosis;

• Given that all chronobiologic analyses can be readily implemented in this era of supercomputers, e.g., as a service offered at the University of Minnesota in the USA, and possibly at the Universities of Florence, Milan and Turin in Italy; of Madrid, Valladolid and Vigo, Spain; and of Bratislava, Slovakia; at Masaryk University in Brno, Czech Republic; at the Institute of Pediatrics of the Russian Academy of Medical Sciences and at Hospital #60 in Moscow, Russia; at Tokyo Women's Medical College, Yamanashi Medical University and the Health Science Center of Kyushu University in Fukuoka, Japan; at the West China University of Medical Sciences in Chengdu, People's Republic of China; and in other locations:

It is proposed:

I. For routine health care practice:

1. To routinely complement the casual measurements of the health care professional by a longitudinal systematic mostly self-monitoring of blood pressure during wakefulness at about 3-hour intervals for a week, with one measurement during midsleep on the first night, with manually operated devices and, as soon as possible, more densely with automatic ambulatory monitors at 15-minute or shorter intervals;

2. To routinely secure a chronobiologic analysis and/or interpretation of time-specified single or serial measurements;

3. To provide educational materials to support self-help and self-responsibility in health care.

II. For long-term implementation:

4. To establish a system for acquiring, distributing and retrieving monitors and for organizing an international data base and chronobiometric analysis center that assure the further accumulation and refinement of reference standards in the light of which the earliest rhythm alteration can be detected and acted upon preventively (rather than only as an after-the-fact "cure");

5. To further develop hardware and software for automatic long-term patient monitoring including elements of windowing, compacting and recycling (40; Figure 18), so that at any time along with a physical examination, the physician, by pressing a button, can access a complete past medical history (in the form of a set of chronome, e.g., rhythm characteristics and trends) of the given person;

6. To concomitantly monitor, at first within the scope of research, variables in the environment (temperature, light intensity, noise, magnetic fields, etc.), to permit the optimization of health, safety and performance by the manipulation of environmental factors acting as synchronizers and/or influencers of chronomes (4), notably of multifrequency physiologic rhythms, and also of trends;

7. To do so for reference value collection from womb to tomb, starting in the neonatal intensive care unit, where the development of premature babies is readily assessable (on the premise that optimal chronome configurations in early extrauterine life may predict risk as a minimum and may prompt as an optimum the institution of measures, yet to be developed, to prevent undesired long-term consequences affecting the rest of the lifespan).

It is resolved

by the New SIRMCE Confederation to approach as an interdisciplinary team the Decision-Making Centers, their Executive Bodies and the general Population to act by chronobiologic education and to raise the consciousness of chronobiology at local, national and international levels, promoting the dissemination of existing chronobiologic knowledge and its implementation in practice, far beyond the illustrative but urgent focus upon dealing with the prevention, diagnosis and timed treatment of blood pressure disorders. This resolution aims to change the status quo by all available means at all levels, including all pertinent entities (Decision Makers, Executive Bodies and general Population, including in particular elected officials).

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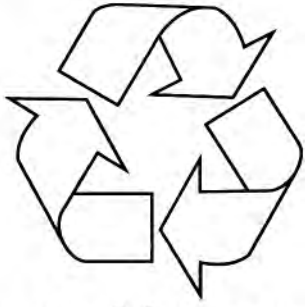
Prof. Olga Quadens (v.s.) and Prof. Miroslav Mikulecky (v.s.) translated this resolution into French and Slovak, respectively; Jarmila Siegelová, Doc. MUDr., DrSc., Associate Professor; Bohumil Fiser, Doc. MUDr., Professor, CSc LF MU, and Jiri Dusek, Dr., Masaryk University, Brno, Czech Republic, translated this resolution into Czech (Rezoluce SIRMCE, AmireporT 2: 105-106, 1995); Miguel A. Revilla, Ph.D., Carmela Rodriguez, M.D., Miguel Revilla Jr., Emilio Revilla, University of Valladolid, Spain, demonstrated family rhythmometry (Familial monitoring of blood pressure and heart rate, in press), produced Chronomova, a computer program for its implementation, and translated the evidence in the figures of this resolution into Spanish with Alvaro Ronco, M.D., National Cancer Registry, Montevideo, Uruguay, who translated the text; Rina M. Zaslavskaya, M.D, Chief of Cardiology, Moscow Hospital #60, Moscow, Russia, and Professor of Hospital Therapeutics, Medical Institute, Aktyubinsk, Kazakhstan; Brunetto Tarquini, M.D., Director, Cattedra di Medicina Interna, Istituto di Clinica Medica Generale e Terapia Medica IV, Università degli

Studi di Firenze, Florence, Italy, had organized consensus meetings with similar resolutions at international conferences, two of them on clinical chronobiology in Monte Carlo (March 17-20, 1988, and April 10-13, 1990) and one in Florence (November 1990) following meetings with presentations on the blood pressure chronome organized by Dr. Pavel Prikryl, Professor of Internal Medicine at Masaryk University, Brno, in Brno (April 9-10, 1990) and in Mostiste (May 22-23, 1991), then Czechoslovakia, soon after the chronome was named and the chronome initiative realized with the late Norberto Montalbetti, Professor of Clinical Chemistry, University of Milan, at the XIV International Congress of Clinical Chemistry held in San Francisco from July 22-26, 1990; Patrick Delmore, BFA, Director of Communications, Medtronic Inc., Minneapolis, Minnesota, USA, graphically prepared the evidence underlying the resolution in the accompanying illustrations.



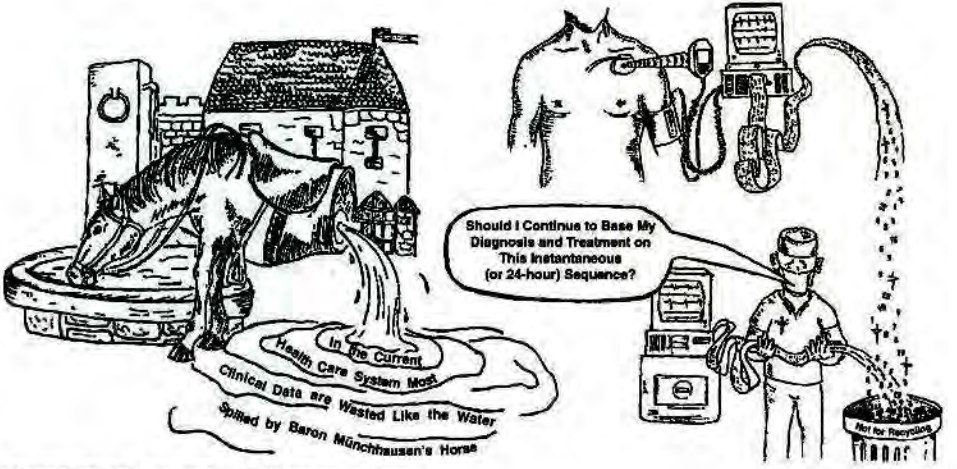
The need for recycling

In human data-gathering, it is an advance to look at circadian patterns, but without a view of the broader chronome of multifrequency rhythms and trends, the analogy to at least some of the water spilling from the midsection of Baron Münchhausen's horse still stands (as long as the information is not further recycled). It seems short-sighted to ask merely whether a given drug raises or lowers the blood pressure when strokes may be prevented by treating an excessive swing in blood pressure around seemingly acceptable 24-hour averages of pressure. The effect of a drug upon the mean is most relevant in the case of an established MESOR-hypertension, an elevation of the rhythm-adjusted mean, assessed from systematic measurements. The MESOR usually provides a more precise and more accurate estimate of location than the arithmetic mean. Dr. Kuniaki Otsuka has demonstrated a very high risk of ischemic stroke and nephropathy when MESOR-hypertension is complicated by a circadian amplitude of blood pressure above the 90th percentile of peers (34). Even for patients with a MESOR of systolic/diastolic blood pressure below 130/90 mm Hg, an excessive circadian amplitude represents a high risk for these conditions (3; cf. also 34). Drug effects upon excessive amplitudes of circadian or circaseptan rhythms, demonstrated by Dr. Yoshihiko Watanabe (Proc. X National Symposium, Indian Society for Chronobiology, Pune, India, August 21-22, 1995, in press), are also important for the prevention of strokes (see pp. 38-41).

INACCURATE SPOTCHECKS ON AVAILABLE, YET WASTED DATA STREAMS

STAFF OR AUTOMATIC TREATMENT ADJUSTMENTS* BASED ON INSTANTANEOUS DATA

RATHER THAN TAKING INTO ACCOUNT THE ENTIRE DYNAMIC HISTORY



* And eventually instrumented self-help for prevention

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Fig. 6

The alternative is recycling, as shown in Figure 18. (See also Figures 9-11)

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Scheme 1. Abstract demonstration of the amplitude on top. This endpoint is a measure of extent of predictable change, recurring with a certain period; when the period is 24 hours, the amplitude can be described as circadian. Note that the total predictable change within 24 hours is the double amplitude. In the also-abstract bottom part of the graph, an excessive amplitude is demonstrated, without any change in overall mean. © Halberg.

Figure 1. Out of 1943 individuals in this study who received a placebo, 48% responded to this "treatment", most of them within less than a year (8). A high percentage of responders to placebo renders it likely that "office hypertension" or "white-coat hypertension" associated with the excitement of one or a few visits to a physician's office leads to the entry into large-scale studies of many false positive cases. A substantial error in diagnosis may well be made, not only at the outset of a study in terms of false positives entering the study, but also at the final evaluation in which the ratio of "cured normotensives" is likely to be complicated by a substantial number of false negative diagnoses. Similar errors in diagnosis are likely to occur in the general practitioner's office when relying on isolated blood pressure readings. © Halberg.

Figure 2. The traditional approach is unsatisfactory in view of the meta-analysis of Wilcox et al. (9) who suggest that clinical practice should not be based on results of such clinical trials. This should be more than a hint to include in future such studies minimal chronobiologic provisions before justifying a total cost of hundreds of millions of U.S. $. © Halberg.

Figure 3. There is a large overlap between the distributions of MESORs (rhythm-adjusted means) of systolic blood pressure of patients conventionally diagnosed as normotensive or hypertensive (11). False positives and false negatives account for about 43% of all conventional diagnoses. © Halberg. Data of I. Kuwajima.

Figure 4. Three around-the-clock blood pressure profiles at intervals of a few weeks on presumably normotensive individuals, lasting between 2 and 4 days, indicate that systolic blood pressure excess is found in 11 of 23 patients (48%), but consistently only in three of them (13%). Since deviations may be detected in one profile but not in all three profiles, blood pressure monitoring over minimal spans of 1 week is suggested (12). © Halberg.

Figure 5. Large decreases in blood pressure can occur spontaneously that warrant the cessation of anti-hypertensive medication. (41) (a). There are also day-to-day changes in circadian amplitude of blood pressure, observed in the case of a 33-year-old neurosurgeon (b) and of a 63-year-old woman under conditions of restricted activity (c). Some of the trends in blood pressure recur every year, as seen in the case of a 70-year-old psychiatrist who shows a circannual

rhythm in his blood pressure with an unusually large amplitude (d). These and other (e.g., Figure 4) results, notably from long-term ambulatory monitoring, underlie the suggestion of a minimal 7-day monitoring span, repeated quarterly for at least one year and, if need be, for even longer-term if not continuous self-monitoring. © Halberg.

Figure 6. Changes in circadian pattern of systolic and diastolic blood pressure and heart rate as a function of age from newborns to centenarians (males). Each curve represents hourly means averaged over all individuals within a given group. Data from the International Womb-to-Tomb Chronome Initiative. © Halberg.

Figure 7. A larger amplitude of blood pressure is found in children with as compared to those without familial antecedents of an elevated blood pressure and related vascular disease. © Halberg.

Figure 8. Reliance on casual blood pressure measurements is undesirable because blood pressure abnormality may occur at odd times of the day or night, when it is unlikely to be checked, as documented here for the diastolic blood pressure of a patient treated once a day in the morning. The automatic, ambulatory monitoring of blood pressure of this patient revealed nightly elevated values in 11 of 12 monitoring spans, each of 24 hours, recognized as excess (blackened area), by comparison of the patient's profile with the time-specified upper 95% prediction limits of peers. Because both the duration and the extent of excess are accounted for, excess is expressed in mm Hg x h; it is calculated herein over consecutive 3-hour spans covering an idealized 24-hour cycle; hence, it is denoted as the "3-hourly fractionated hyperbaric index". Such a diastolic blood pressure excess for several hours around midnight in this diurnally active, nocturnally resting man should prompt concern and added timed treatment. © Halberg.

Figure 9. Relative risk of ischemic stroke and nephropathy in patients with an excessive circadian blood pressure amplitude by comparison to risk of patients with an acceptable circadian blood pressure amplitude. For different classes of the 24-hour mean (MESOR) of systolic blood pressure, even below 130 mm Hg, an excessive circadian blood pressure amplitude is associated with a relative risk larger than 1, that is with an increase in risk of ischemic stroke and nephropathy. This increase in risk is statistically significant for normotensive patients, as illustrated by the fact that the 95% confidence interval does not overlap 1 (equal risk). A relative risk of 3.4 represents an increase in risk by 240% (e.g., for the case of ischemic stroke of patients with a MESOR of systolic blood pressure between 140 and 150 mm Hg). © Halberg. Data of K. Otsuka.

Figure 10. Relative risk of ischemic stroke for various risk factors computed as the ratio of the incidence of ischemic stroke that

occurred in patients presenting with the tested risk factor by comparison with that in patients not presenting with the tested risk factor. Results of a 6-year prospective study on 297 patients indicate that the risk associated with an excessive circadian blood pressure amplitude is larger than that of all other risk factors considered (obesity, high cholesterol, male gender, drinking alcohol, having familial antecedents with high blood pressure or adverse vascular event, smoking, age above 60 years, and an elevated mean blood pressure value). As compared to patients with an acceptable circadian blood pressure amplitude, patients with an excessive circadian diastolic blood pressure amplitude have a risk of ischemic stroke 8.2 times larger (i.e., they have an increase in risk of 720% to develop an ischemic stroke). © Halberg. Data of K. Otsuka.

Figure 11. Relative risk of ischemic stroke associated with an excessive circadian blood pressure amplitude. In order to test for any interaction of the risk from an excessive circadian blood pressure amplitude with that from other known risk factors (obesity, high cholesterol, male gender, smoking, consumption of alcohol, familial antecedents, old age and MESOR-hypertension), the relative risk was computed in subpopulations not presenting with the tested risk factor other than the circadian blood pressure amplitude. In each case, an excessive circadian blood pressure amplitude represents a larger risk factor for ischemic stroke than the tested risk factor. The fact that the 95% confidence intervals almost invariably do not overlap 1 indicates that an excessive circadian blood pressure amplitude raises the risk of ischemic stroke statistically significantly, irrespective of the effect of the other risk factor tested. © Halberg. Data of K. Otsuka.

Figure 12. Separate comparisons of results from once-traditional treatment with equal doses three times a day versus time-targetted (chrono-)therapy for propranolol, clonidine, and a-methyldopa: each comparison involves 40 patients, randomly assigned to either traditional treatment or chronotherapy (20 patients per group). Chronotherapy consists of drug administration 1.5 to 2 hours before the circadian peak(s) in systolic blood pressure, determined after synchronization for 3 days of each untreated patient with the hospital routine. The single initial dose selected for chronotherapy consisted of 50 to 70% of the dose used for traditional treatment. With this "handicap for chronotherapy design", patients were matched by stage of disease and, as possible, by age, gender, and clinical signs. Daily morning blood pressure measurements, and a diary by the patient listing any headache, chest pain, dizziness, palpitation, insomnia, or other symptoms helped in assessing the time to the appearance of the desired effect and the incidence of side effects, respectively. The 24-hour profile of systolic blood pressure was repeated after 2 weeks, the dose of the drug being changed in the interim if and as needed. A clinically stable hypotensive effect was detected earlier for chronotherapy as compared with traditional ther-

apy, with, on the average, smaller doses and greater efficacy. Side effects from treatment were reduced in the case of chronotherapy (35). These pioneering results must not be extended to ACE inhibitors and calcium antagonists, drugs with other chronopharmacokinetics. The design in these studies is best replaced by longitudinal monitoring (Figure 18). © Halberg. Data of R. Zaslavskaya.

Figure 13. A 33-year-old neurosurgeon diagnosed conventionally as moderately hypertensive reveals large variation and the need for dense and long sampling in order to approach the dilemma whether to treat or not to treat. Original data of Dr. J.C. Menéndez analyzed by Dr. A. Portela. © Halberg.

Figure 14. The conventional interpretation of the data collected during office hours by the 33-year-old neurosurgeon referred to in Figure 13 leaves one in a quandary if only 56% of the measurements are acceptable but 44% are found to be elevated over a 23-day monitoring span. © Halberg.

Figure 15. The decision to treat or not to treat the 33-year-old neurosurgeon referred to in Figures 13 and 14 is the more difficult since during office hours most of his measurements (77%) are acceptable on one day but are invariably too high on another day. © Halberg.

Figure 16. Control charts of daily mean values of blood pressure and heart rate computed on all data collected at 15-minute intervals are shown with a shaded decision interval. While the series of daily means is proceeding "in control" (i.e., at the pre-treatment mean level), the cusum comprises two line graphs that generally stay within the "decision interval" limits, which are plotted here as the horizontal lines at 4.4 and -4.4 SD. Two curves signal increase and decrease in mean, respectively. When the dashed curve breaks out of the decision interval boundary, it provides the rigorous validation of the decrease in daily blood pressure mean. The time at which the mean changed is estimated by tracking the line segment leading to the breakout back to the last occasion on which it lay on the horizontal axis. Thus, in the case of systolic blood pressure, the breakout occurs on day 30 (16 days after the start of lisinopril treatment) and the shift in pressure is estimated to have occurred on day 22 (8 days after lisinopril treatment started). © Halberg.

Figure 17. Control charts of decimated time series based on single daily measurements (top, left and right; bottom left) or on a mean of three daily measurements (bottom right) of blood pressure and heart rate are shown with shaded decision intervals for a shift in location index. Whereas single daily measurements are insufficient to reach a consistent decision whether lisinopril was effective, such a conclusion can be made when three daily measurements are used. © Halberg.

Figure 18. In many circumstances the data are collected or are amenable to being collected over time but the information is discarded after a mere visual inspection of a monitor's recording. Adding chronobiologic analytical procedures for the on-line processing and interpretation of the data would provide individual reference standards for rhythms with lower and lower frequencies while also providing continued check-ups capable of detecting the earliest rhythm alterations indicative of a heightened risk and thus enabling the prompt institution of treatment when indicated. (The analogy that a single 24-hour cycle from a circadian viewpoint corresponds to the radial pulse based on a single heartbeat [42] has now been shared by others [43].) © Halberg.

[1]Presented by Franz Halberg and Germaine Cornélissen on March 17, 1995, at a meeting in the Royal Crown Hotel, Brussels, of the New SIRMCE (International Society for Research on Civilization Diseases and the Environment) Confederation; discussed on that day, when Douglas Wilson moved that the resolution be made into an action item of the Society for presentation and implementation at the World Health Organization and other bodies specifically concerned with blood pressure disorders. The motion by Dr. Wilson and the resolution as a whole were unanimously approved after further discussion on March 18, 1995, at the conclusion of the SIRMCE meeting.

[2]The science of chronobiology (1-3) quantifies the time structure characterizing each physiologic variable, its genetically anchored and mostly environmentally synchronized chronome (4). Thereby, one gains new information and thus a new dimension to the care of one's health and the integrity of one's environment. The importance of chronobiologic information has been compared with the importance of the energy released by splitting the atom (3). This science ushers in a new era by allowing one to do more than asking only whether a time-unspecified measurement or a series of such casual measurements or even a series of systematic measurements covering a day or a week is too high or too low. Instead, one can rely on a rhythm-adjusted mean (the MESOR) that as compared to the arithmetic mean is more accurate and more precise. As a dividend (which may be more important under certain conditions than the best average value), chronobiology also provides new information on the extent of predictable since rhythmic changes (the double amplitudes) and on the timing of regularly recurring high values within anticipated cycles (the acrophases), and on other indices of random or overall variability such as the standard deviation (SD).

The new information on acrophase applies to the treatment of most if not all diseases, so that timing is added to dosing, for instance in treating cancer or blood pressure disorders. A very great promise of the new endpoints, the amplitude in particular, lies in the cerebro-, reno- and cardiovascular fields. Relatively inexpensive, manually activated devices, e.g., for blood pressure measurement, have been available for a long time. New automatic monitoring and treatment devices are also available and can be further perfected or will become available as hemodynamic analyzers in the near future, and await application in preventive as well as curative health care.

For the case of the monitoring of environmental integrity, variables such as peak expiratory flow could be measured and the series analyzed chronobiologically with instrumentation available only for manual measurement and not yet for automatic ambulatory monitoring. Whether the physiologic monitoring is done by self-measurements or by automatic devices, emphasis can be placed on self-help and self-responsibility in health and environmental care, achieved via a chronobiologic analysis with refined endpoints. The data can be interpreted in the light of time-specified reference values derived from large data archives that have accumulated over the last four decades at the Chronobiology Laboratories of the University of Minnesota, Minneapolis.

[3]Including a former head of the Hypertension-Endocrine Branch of the U.S. National Institutes of Health (NIH) and subsequent Director of the Clinical Center at NIH, as well as other senior professors of internal medicine (14-16).

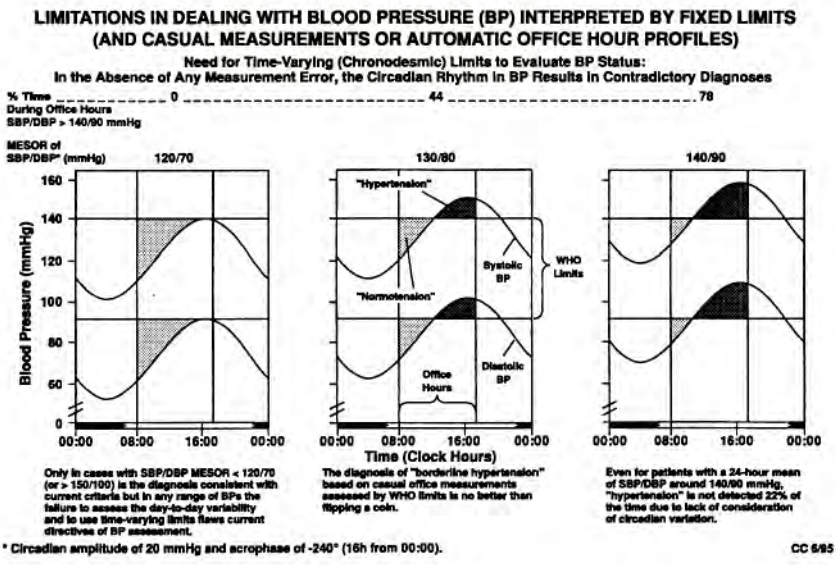
Table 1

FIXED THRESHOLDS[1] CAN RENDER THE OFFICE BLOOD PRESSURE (BP) EQUIVALENT TO FLIPPING A COIN; SO DOES VARIABILITY (AS SHOWN ELSEWHERE)

When the 24-hour average of blood pressure (BP) is 125/75 (systolic [S]/diastolic [D]), very many office measurements will exceed limits

S/DBP MESOR (mm Hg)	Daily Span (hours) with SBP/DBP>140/90 mm Hg	Measurements > 140/90 mm Hg (%)[2] during 24 hours	during office hours
120/70	0	0	0
125/75	5.52	23.00	**41.78**
130/80	8.00	33.33	**44.44**
135/85	10.07	42.00	67.06
140/90	12.00	50.00	77.78

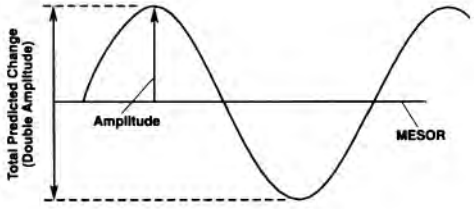
1. Best replaced by chronodesms, i.e., 90% peer prediction limits for single samples and chronome characteristics.
2. Percentage of BP values above or below NIH-WHO-WHL limits of 140/90 mm Hg (systolic/diastolic BP) expected to occur within a 24-hour span or during office hours (08:00-17:00), assuming a circadian amplitude of 20 mm Hg, near the upper 95% prediction limit of healthy peers and an average acrophase in mid-afternoon (around 16:00), with SBP MESORs ranging from 120-140 and DBP MESORs from 70-90 mm Hg.



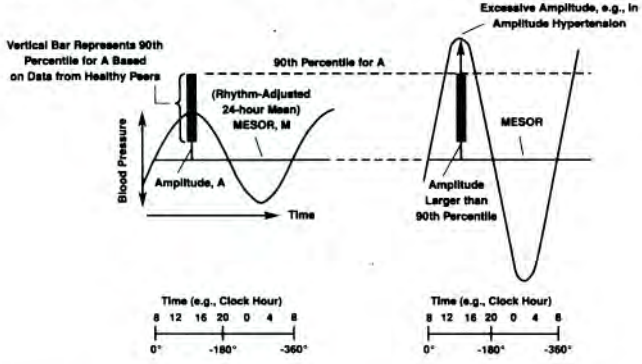
B05

Amplitude, A

Half of Total Predictable Change in Rhythm, Defined by Rhythmic Function Fitted to Data; Expressed in Original or "Relative" Units, e.g., as Percentage of Series Mean or MESOR.



Excessive Circadian Blood Pressure Amplitude (e.g., Circadian Amplitude Hypertension)*

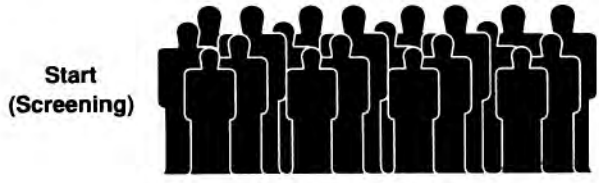


* Amplitude deviating outside reference limits.

CC 9/94

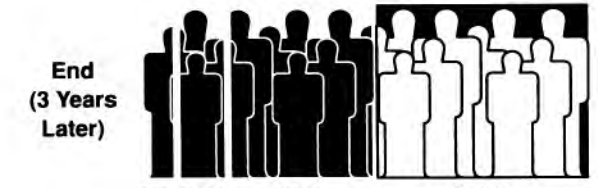
A larger circadian amplitude of blood pressure characterizes newborns at term and adolescents 1) with a positive vs. negative family history of high blood pressure and/or related vascular complications and 2) with vs. without exposure in utero to betamimetic drugs. In adulthood, a larger circadian amplitude of blood pressure is found in an intermediate group formed on the basis of cardiac left ventricular mass, in the absence of any elevation in blood pressure MESOR and 2) an excessive circadian blood pressure amplitude carries a very large risk of ischemic stroke and nephropathy (Figures 9-11, pp. 29-31).

"CONTROL" GROUP (N = 1943) OF A THERAPEUTIC TRIAL IN MILD HYPERTENSION*



Range of DBP (mmHg) 95 - 109 (Mean, $\bar{y}$ = 102)

After 3 Years Of Placebo Treatment



8%	12%	32%	48%**
Ischemic Coronary Heart Disease Or Stroke	> 109 DBP (mmHg)	95 - 109 DBP (mmHg)	< 95 DBP (mmHg) $\bar{y}$ = 91

* Cost: $60 million.

** Those "cured" with placebo include placebo-responders and/or those falsely diagnosed as "hypertensive" at the start and/or falsely diagnosed as normotensive at the end of study.

CC 9/92

Fig. 1

QUO USQUE TANDEM: TREATMENT TRIALS OF "BLOOD PRESSURE ELEVATION"*

#	Study	# and Gender of Patients	Blood Pressure Systolic/Diastolic (mmHg)	Reference
1	U.S. Veterans Administration	523 M	/ ≥ 90	JAMA 202: 1028-1034, 1967 JAMA 213: 1143-1152, 1970
2	U.S. Hypertension Detection and Follow-Up Program	10,940 M & F	/ > 90	JAMA 242: 2562-2571, 1979 JAMA 247: 633-638, 1982
3	Oslo	785 M	150-179 / ≥ 100	Am. J. Med. 69: 725-732, 1980
4	Australian	3,427 M & F	/ > 95-109	Lancet I: 1261-1267, 1980 Circulation 69: 668-676, 1984
5	U.S. Multiple Risk Factor Interventions Trial	12,866 M	/ > 90-115	JAMA 248: 1465-1477, 1982
6	European Elderly	940 M & F	/ > 90-119	Lancet I: 1349-1354, 1985
7	International Prospective Primary Prevention Study	6,537 M & F	/ > 100-125	J. Hypertension 3: 379-392, 1985
8	British MRC	17,354 M & F	/ > 90-109	Br. Med. J. 291: 97-104, 1985
9	Gothenburg	635 M	> 175 / or / > 115	Lancet I: 1-5, 1978

* Condensed from a classical meta-analysis by Wilcox RG, Mitchell JRA, Hampton JR: Treatment of high blood pressure: should clinical practive be based on results of clinical trials? Br. Med. J. 293: 433-437, 1986.

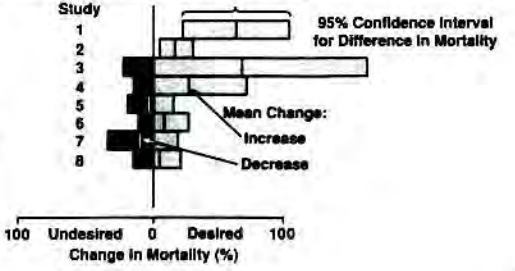
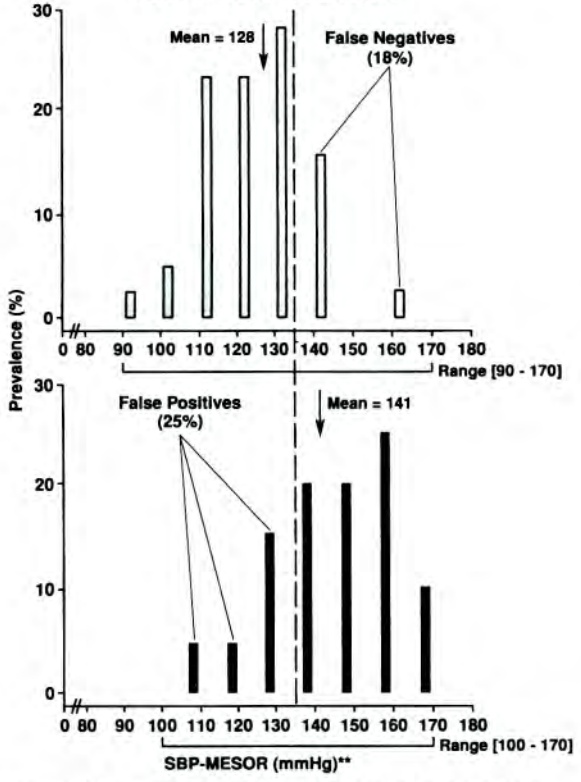


Fig. 2

808

ELDERLY CONVENTIONALLY DIAGNOSED AS "NORMOTENSIVE" (□; N = 39) AND "HYPERTENSIVE" (■; N = 20) SHOW ALMOST IDENTICAL RANGES OF SYSTOLIC BLOOD PRESSURE MESORS*



* Misdiagnoses by loose World Health Organization criteria applied to casual measurements of 62 - 90 year old men and women. Systematic chronobiologic self-monitoring (manually or, preferably automatically) by everybody is needed.

** MESOR = rhythm-adjusted 24-hour mean.

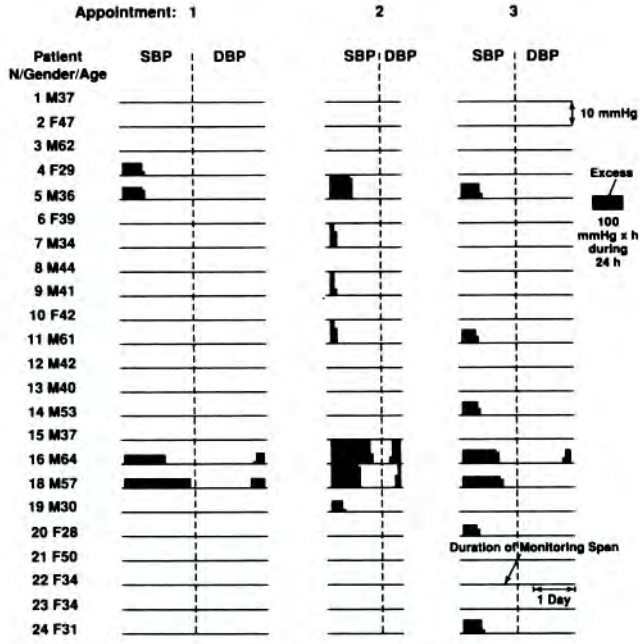
CC 3/93

Fig. 3

Original data of I. Kuwajima

Blood pressure disorder missed in 4-day around the clock record in patients 7, 9, 11, 14, 19, 20 and 24

BLOOD PRESSURE (BP) *EXCESS* IN 23 PRESUMABLY NORMOTENSIVES MONITORED FOR 9 DAYS*



* Each for 4, 2 and 3 days bracketing three consecutive dental appointments; results of BP excess shown only for patients with excess above 50 mmHg x h during 24 h. SBP = systolic BP; DBP = diastolic BP.

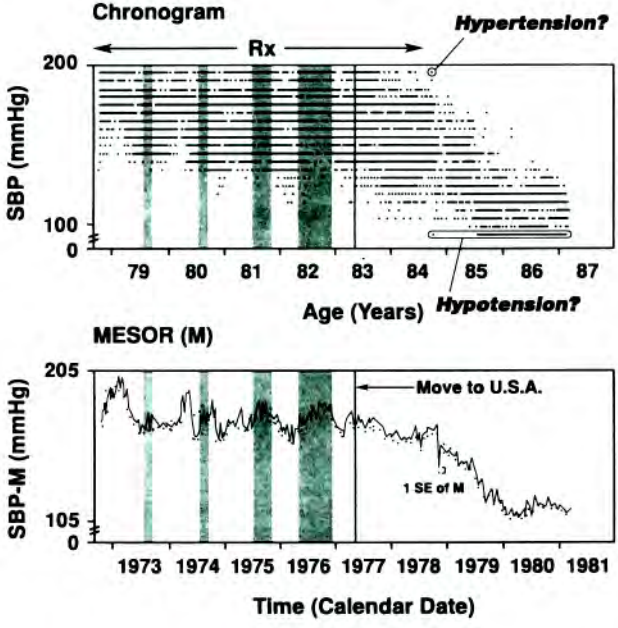
CC 10/93

Fig. 4

Original data of F. Raab

C04

SELF-MEASUREMENTS IN ELDERLY WOMAN REVEAL DRASTIC CHANGES IN SYSTOLIC BLOOD PRESSURE (SBP) WITH AGE*



* 14,046 SBP measurements; serial section at trial period of 24 hours over non-overlapping 168-hour intervals. Transmeridian flights over 7 time zones are shaded; antihypertensive medication up to 1978

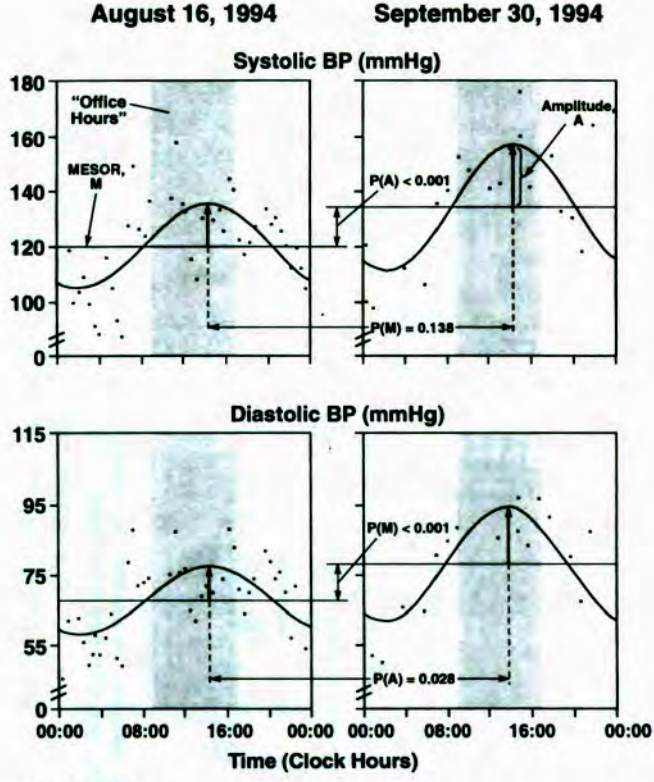
CC 11/91

Fig. 5a

Original data of M. Haus

22650-09

LARGE DAY-TO-DAY VARIABILITY IN CIRCADIAN CHARACTERISTICS OF BLOOD PRESSURE (BP) REVEALS INSUFFICIENCY OF PROFILE LIMITED TO 24 HOURS*



* JCM (M, 33y)
1. From test of equality of MESORs; 2. From test of equality of circadian amplitudes.

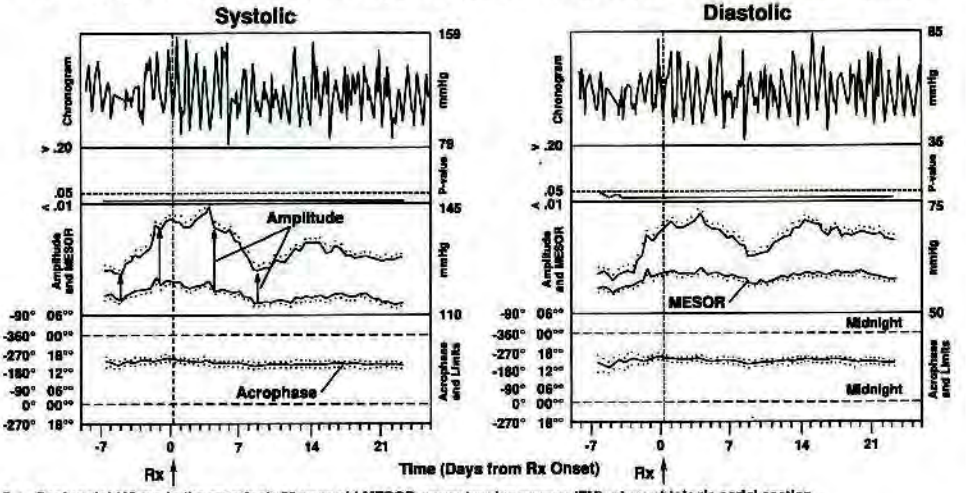
CC 12/94

Fig. 5b

Original data of J. C. Menendez, analyzed by A. Portela

DAY-TO-DAY VARIABILITY IN BLOOD PRESSURE AND ITS CIRCADIAN CHARACTERISTICS

Note Differences in Amplitude, Even Under Conditions of Restricted Activity in the Face of Relatively Stable MESOR and Acrophase (in the Presence or Absence of Treatment, Rx)



Rx = Penbutolol (40 mg in the morning); 63-year-old MESOR-normotensive woman (EH); chronobiologic serial section with fit of a 24-h cosine curve to data intervals of 120 h displaced in 12-h increments.

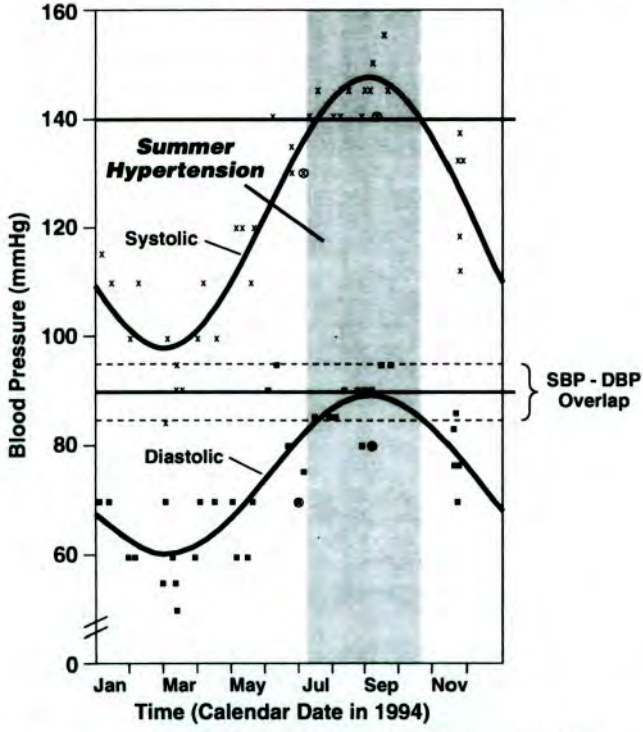
CC 4/95

Fig. 5c

28990-12

22656-06

LARGE CIRCANNUAL AMPLITUDE [AWAKENING SYSTOLIC BLOOD PRESSURE (SBP) IN ONE SEASON LOWER THAN DIASTOLIC (D) BP IN ANOTHER SEASON] WARRANTS DIFFERENT HANDLING IN SUMMER VERSUS WINTER*



N = 37	P-Value	Percent Rhythm	MESOR ± SE	Double Amplitude ± SE	Acrophase (95% CI)
SBP	< 0.001	87	122.5 ± 1.2	48.8 ± 3.5	Aug 26 (Aug 17, Sep 4)
DBP	< 0.001	72	74.6 ± 1.2	28.8 ± 3.3	Sep 4 (Aug 17, Sep 15)

* Large amplitude of circannual BP rhythm in untreated patient (GN, M, 70 y) self-measuring immediately after awakening; ⊠, ⊗ measurements taken in physician's office in the afternoon; SE = standard error; CI = confidence interval.

CC 12/94

Fig. 5d

The chronome of a variable such as blood pressure or heart rate is a genetically anchored time structure of multifrequency rhythms and trends as well as residual noise. Circadian variation undergoes changes in prominence with age. Trends such as a blood pressure increase or heart rate decrease are also seen early in life. Infradians are then also more prominent than circadians. The reverse holds true with increasing age.

TIME COURSE OF BLOOD PRESSURE (BP) AND HEART RATE (HR) AS A FUNCTION OF AGE

MALES

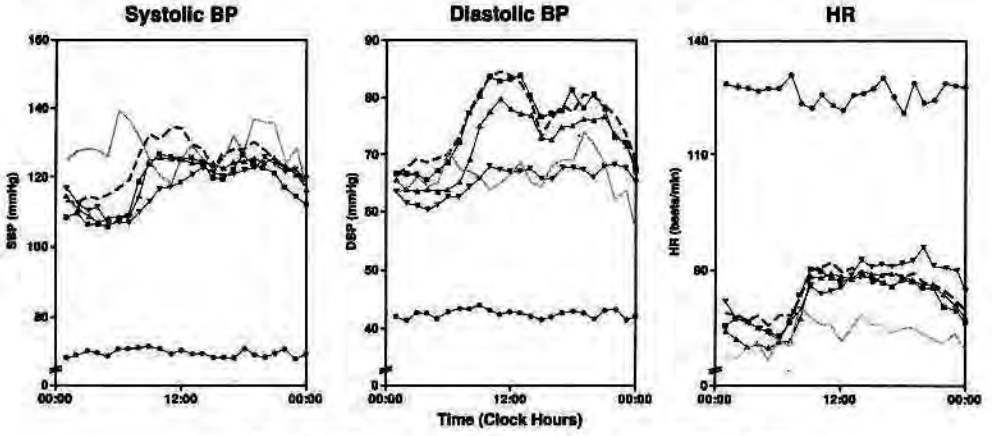
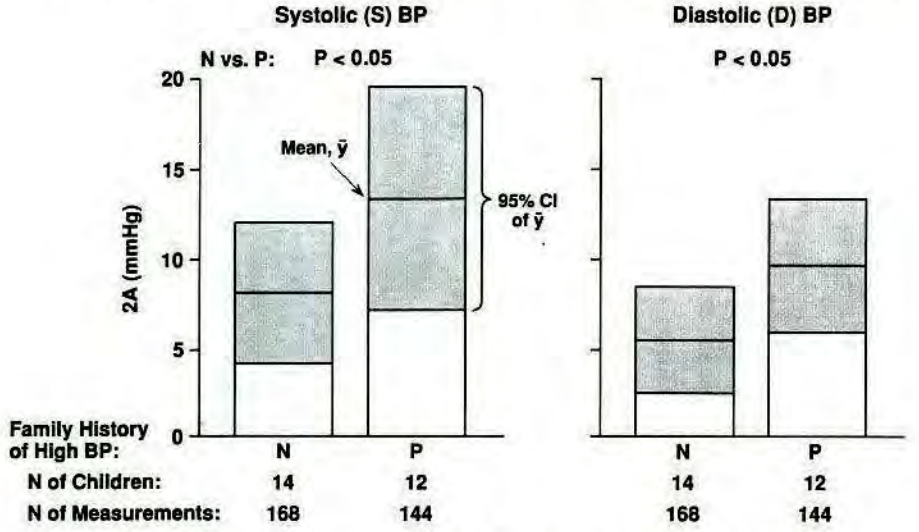


Fig. 6

A03

CHILDREN'S BLOOD PRESSURE (BP) CHRONOME AND CARDIOVASCULAR DISEASE RISK*



* Larger circadian amplitude (A) of SBP and DBP of 6-7 year old children with a positive (P) vs. a negative (N) family history of high BP; data of Wan et al. (1994).

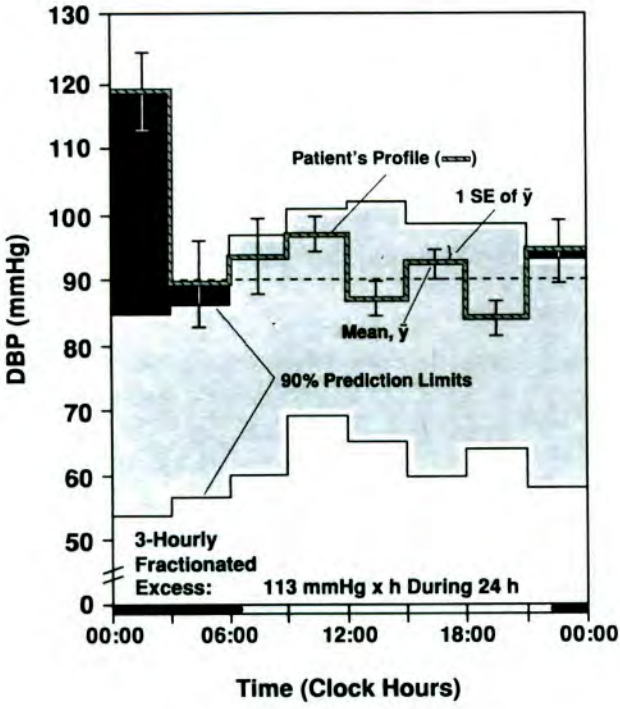
CC 2/94

Fig. 7

Reliance only on clinic measurements can be misleading. Measurements are taken in the office only.

D01

ODD-TIME DIASTOLIC BLOOD PRESSURE (DBP) EXCESS (■) WITH TREATMENT IN THE MORNING*



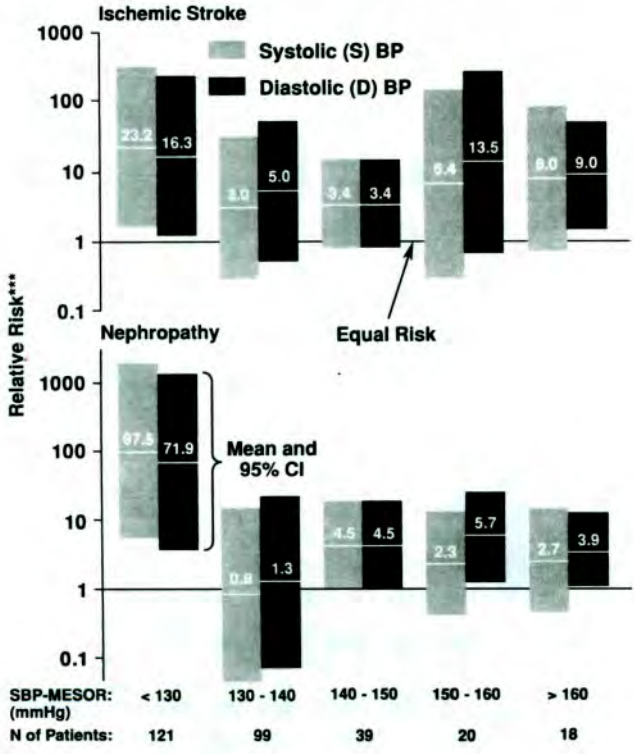
* DJ (M, 78-y) taking "daily" 10 mg Vasotec (ACE-inhibitor); sizeable DBP excess at times when it would usually be missed.

CC 3/93

Fig. 8

D04

AN EXCESSIVE CIRCADIAN BLOOD PRESSURE (BP) AMPLITUDE (A)* IS A RISK FACTOR FOR ISCHEMIC STROKE AND NEPHROPATHY INDEPENDENT FROM THE 24-HOUR MEAN (MESOR)**



* Above 90th percentile of peers.

** Results of 6-year follow-up study of 297 patients.

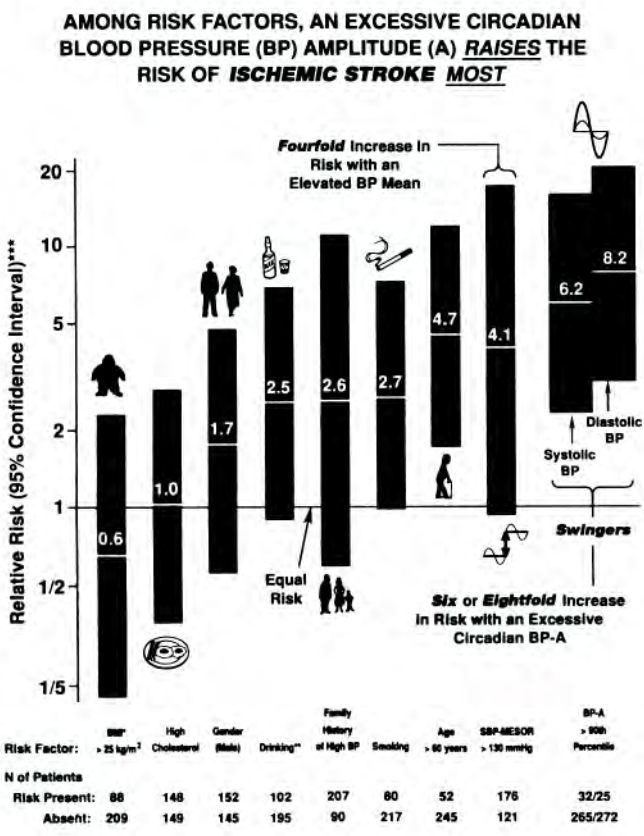
*** Relative Risk (RR) is risk of patients with an excessive circadian BP-A relative to risk of patients with an acceptable circadian BP-A (whose RR = 1).

CC 11/94

Fig. 9

Original data of K. Otsuka (34)

An excessive circadian amplitude of diastolic blood pressure represents a 720% increase in risk of ischemic stroke (see last column on the right)



* BMI (Body Mass Index) correlates positively with BP-MESOR.

** Drinking increases BP-A.

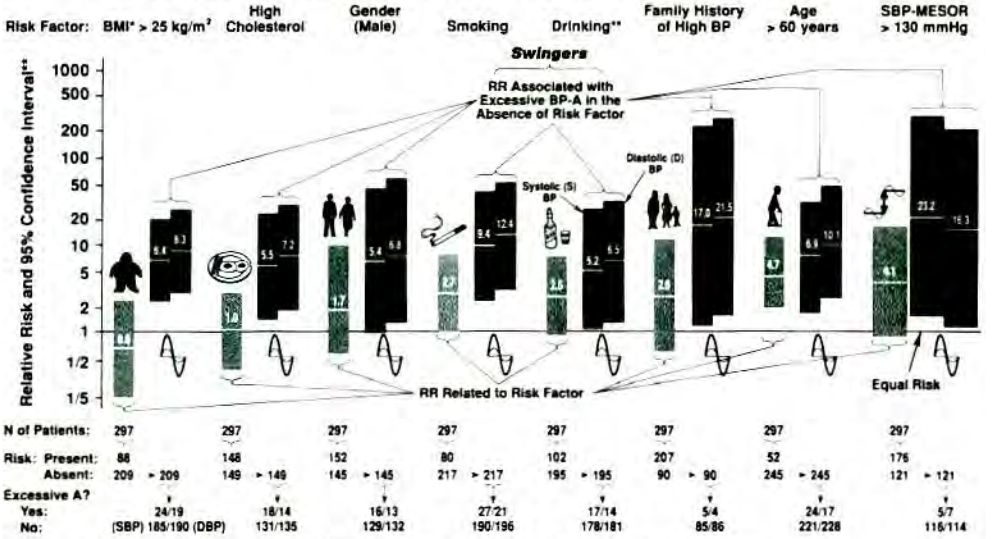
*** Relative Risk (RR) is risk of patients with risk factor (e.g., smoking or excessive BP-A) present relative to risk of patients with risk factor absent (whose RR = 1) computed as a ratio of incidences.

CC 11/94

Fig. 10

Original data of K. Otsuka (34)

AN EXCESSIVE CIRCADIAN BLOOD PRESSURE (BP) AMPLITUDE (A) IS A LARGER RISK FACTOR FOR ***ISCHEMIC STROKE*** THAN OTHER KNOWN RISK FACTORS



* BMI (Body Mass Index) correlates positively with BP MESOR; ** Drinking is associated with increased BP-A.

** Relative Risk (RR) is risk of patients with risk factor (e.g., smoking or excessive BP-A) present relative to risk of patients with risk factor absent (whose RR = 1), computed as a ratio of incidences.

CC 11/94

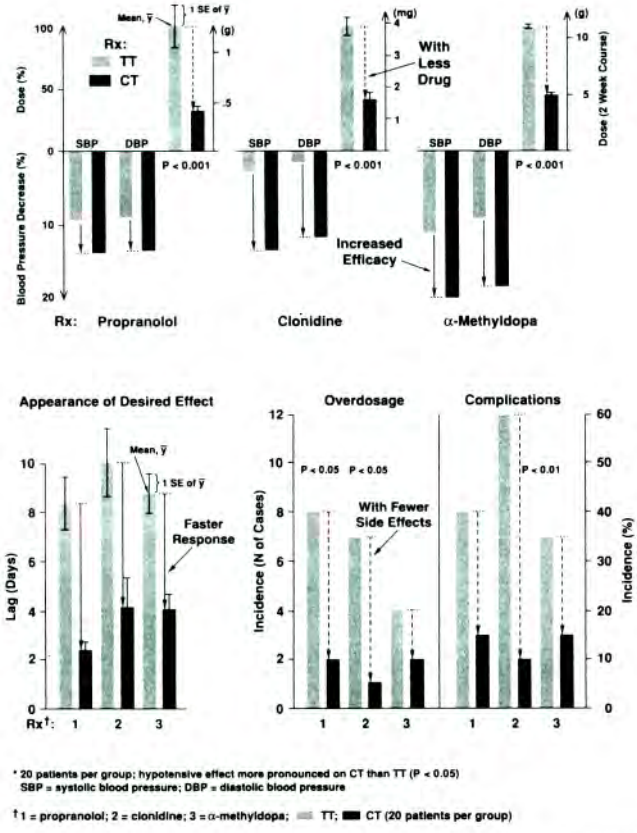
Fig. 11

D11

Original data of K. Otsuka (34)

D13

EFFICACY, SAFETY AND COST-EFFECTIVENESS OF CHRONOTHERAPY (CT) VERSUS TRADITIONAL THERAPY (TT) WITH THREE ANTI-HYPERTENSIVE DRUGS*



* 20 patients per group; hypotensive effect more pronounced on CT than TT ($P < 0.05$)
SBP = systolic blood pressure; DBP = diastolic blood pressure

† 1 = propranolol; 2 = clonidine; 3 = α-methyldopa; TT; CT (20 patients per group)

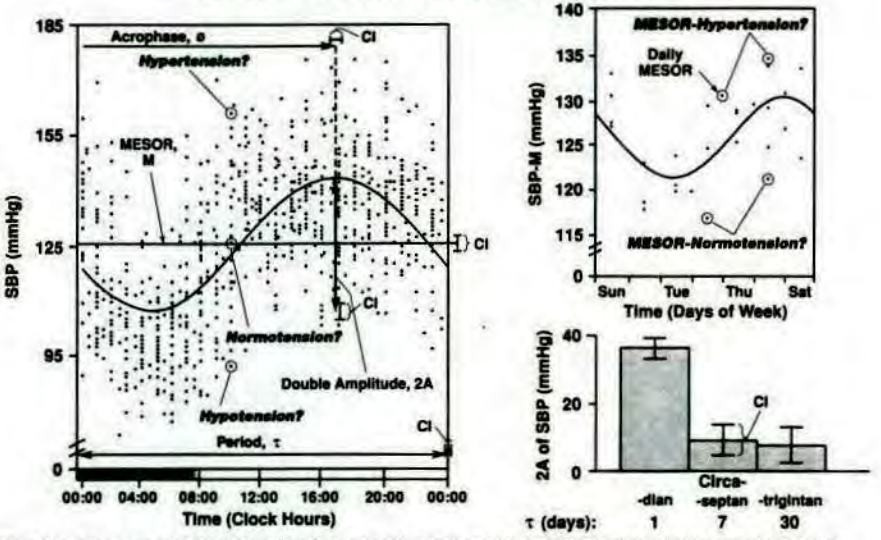
CC 10/91

Fig. 12

Data of R. Zaslavskaya.
For other aspects of chronotherapy, see pp. 36, 37 and 41.

Need for systematic chronobiologic long-term self-surveillance

HYPERTENSION AND NORMOTENSION AT SAME CLOCK-HOUR OR EVEN IN 24-HOUR AVERAGE ON SAME DAY OF WEEK*



* Systolic Blood Pressures (SBP) at 30 or 60 minutes for 30 days (n = 782) over idealized day (left) or week (top right) reveal relative prominence of circadian vs. infradian components (bottom right); JCM (M, 33y, untreated); CI = 95% confidence interval.

CC 2/95

Fig. 13

25557-01

Flipping a Coin

Of 230 ambulatory blood pressures (BP) measured automatically during 23 days, about half are acceptable (56%) and half unacceptable (44%)*

CLASSIFICATION FOR BP IN POPULATION

SBP DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	Optimal	Normal	High Normal	High
80-84	Normal	Normal	High Normal	High
85-89	High Normal	High Normal	High Normal	High
≥ 90	High	High	High	High

(JCM, %/class)

SBP DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	11	16	14	6
80-84		1	10	10
85-89		1	3	14
≥ 90				14

Total High: 44%

STAGES OF HIGH BP

SBP DBP mmHg	< 140	140-159	160-169	180-...
< 90	No HBP	1	2	3-4
90-99	1	1	2	3-4
100-109	2	2	2	3-4
110-...	3-4	3-4	3-4	3-4

SBP DBP mmHg	< 140	140-159	160-179	180-...
< 90	56%	29	1	
90-99		11	3	
100-109				
110-...				

* Subject is a 33-year-old neurosurgeon (JCM), right. Interpretation by prevailing criteria (left) of NIH-NHLBI (No HBP = no high BP; 1-4 = hypertension stage 1-4), 5th report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (NIH Publication No 93-1088).
Measurements by ABPM-630 Colin Medical Instruments (Komaki, Japan) from 09:00 to 17:00 during week-days, to simulate office hours.

CC 3/95

27057-1

Fig. 14

A single 24-hour blood pressure (BP) profile: fool's gold, not gold standard*

AUGUST 16, 1994 (N = 13) — SEPTEMBER 28, 1994 (N = 12)

CLASSIFICATION FOR BP

SBP DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	O 15%	N 15%	HN 47%	H
80-84	N	N	HN	H 8%
85-89	HN	HN	HN	H 15%
≥ 90	H	H	H	H

SBP DBP mmHg	< 120	120-129	130-139	≥ 140
< 80	O	N	HN	H
80-84	N	N	HN	H
85-89	HN	HN	HN	H 63%
≥ 90	H	H	H	H 37%

Totals: N = 77% H = 23% — **Normotension?**

N = 0% H = 100% — **Hypertension?**

STAGES OF HIGH BP

SBP DBP mmHg	< 140	140-159	160-169	180-...
< 90	n 77%	h1 23%	h2	h3-4
90-99	h1	h1	h2	h3-4
100-109	h2	h2	h2	h3-4
110-...	h3-4	h3-4	h3-4	h3-4

SBP DBP mmHg	< 140	140-159	160-179	180-...
< 90	n	h1 63%	h2	h3-4
90-99	h1	h1 25%	h2 12%	h3-4
100-109	h2	h2	h2	h3-4
110-...	h3-4	h3-4	h3-4	h3-4

* Measurements during simulated office hours (09:00-17:00) with ambulatory monitor by 33-year-old man (JCM) on two different days. O = optimal; N = normal; HN = high normal; H = high in classification of BP for adults age 18 years and older; n = no high BP; h1-h4 = hypertension stage 1-4 in classification of stages of high BP for adults age 18 years and older according to NIH-NHLBI, 5th report of the Joint National Committee on detection, evaluation, and treatment of high BP (NIH Publication No 93-1088).
Measurements by ABPM-630 Colin Medical Instruments (Komaki, Japan).

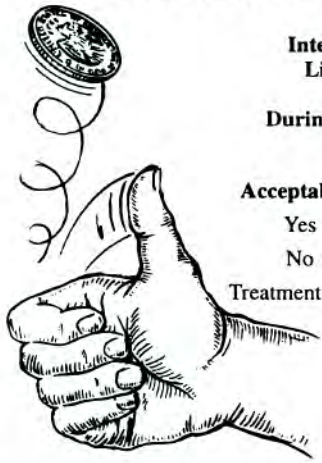
CC 3/95

27057-2

Fig. 15

There is no alternative to a systematic chronobiologic blood pressure self-surveillance, notably in "borderline hypertension".

ORATIO CONTRA MOREM PRÆVALENTEM ET PRO CHRONOBIOLOGICA RATIONE AD PRESSIONEM SANGUINIS CURANDAM



Interpretation by 140/90 mmHg (Systolic/Diastolic) Limit of Automatic Ambulatory Blood Pressure Measurements on JCM, M, 33 yrs During Office Hours Only (09:00 – 17:00 on Weekdays)

Acceptable?	94/08/16	94/09/28	Over 23 Days
Yes	77%	0%	56%
No	23%	100%	44%
Treatment (Rx)?	No	Yes	Non-Drug Rx with Further Monitoring

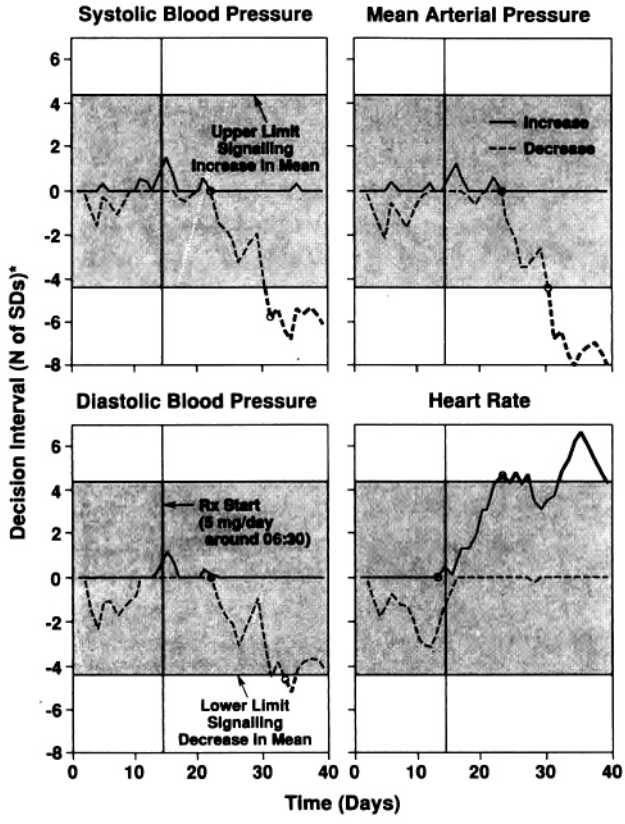
27432-5

CC 3/95

Two tables on the left of Figure 14 show the current classification used by the U.S. National Institutes of Health, the World Health Organization and the World Hypertension League, considering that systolic/diastolic blood pressure values below 140/90 mm Hg are acceptable. On the basis of this classification, the tables on the right of Figure 14 and in Figure 15 summarize blood pressure readings obtained during office hours from the automatic ambulatory monitoring of the same subject. Over a 23-day monitoring span, 56% of measurements during office hours are acceptable. On one day (August 16, 1994), 77% of office-hour measurements are acceptable, whereas on another day (September 28, 1994), none of the measurements (0%) are acceptable. This is a factual illustration of the theoretical computation in Table 1 (p. 16) leading to the inference that a single 24-hour profile can be equivalent to flipping a coin.

A06

INDIVIDUALIZED ASSESSMENT OF A PATIENT'S RESPONSE TO LISINOPRIL (Rx) BY CUSUM (FH, M, 74y)



* Standard Deviation from CUSUM: If there is displacement of 1 SD, it would be diagnosed by a slope of (1 - 0.5 =) 0.5 SD.

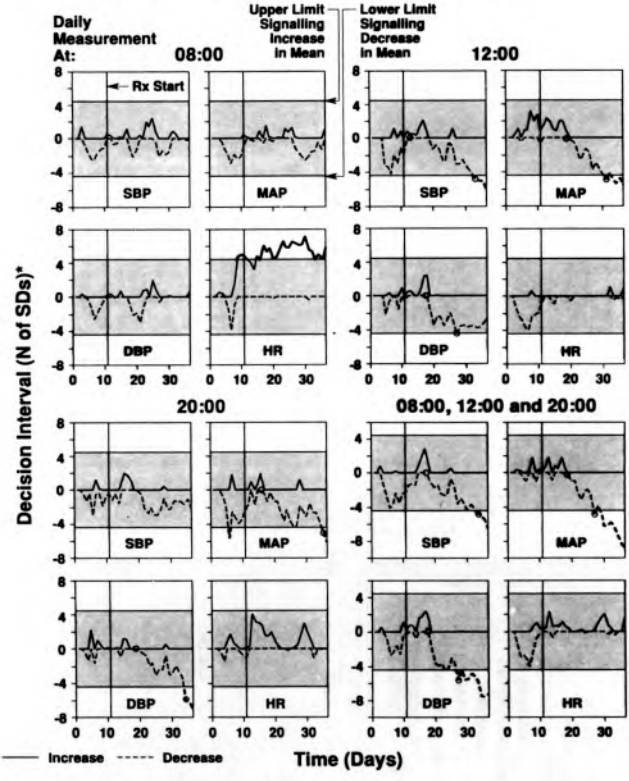
CC 6/94

Fig. 16

Note break-out from shaded decision interval of lower or upper curve signalling blood pressure decrease and heart rate increase, respectively.

A computer-implemented control chart can be based on minimal daily sampling specified after decimation of a denser record.

WHEREAS SINGLE DAILY MEASUREMENTS DO NOT RELIABLY ASSESS INDIVIDUAL'S (FH, M, 74y) RESPONSE TO TREATMENT (Rx), A FEW STRATEGICALLY PLACED VALUES LEND THEMSELVES TO A CHRONOBIOLOGIC ANALYSIS AND CAN ACHIEVE THE TASK COST-EFFECTIVELY



*** Standard Deviation from CUSUM: If there is displacement of 1 SD, it would be diagnosed by a slope of (1 - 0.5 =) 0.5 SD; Rx = lisinopril (5 mg/day, on awakening, in this case around 06:30).**

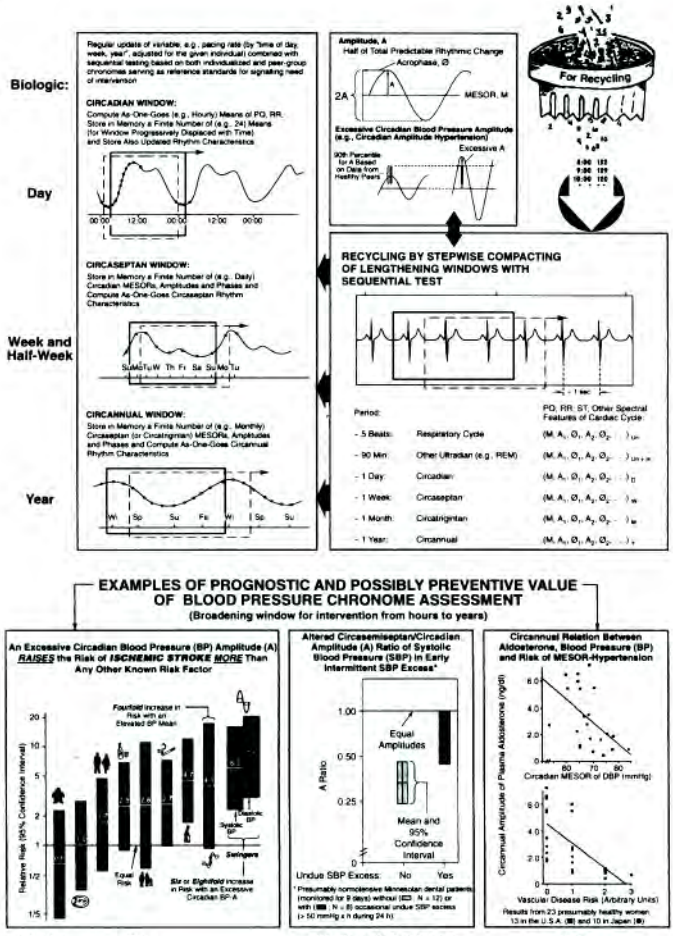
CC 8/94

Fig. 17

CHRONOBIOLOGIC ANSWERS:

Monitoring, analyzing and recycling

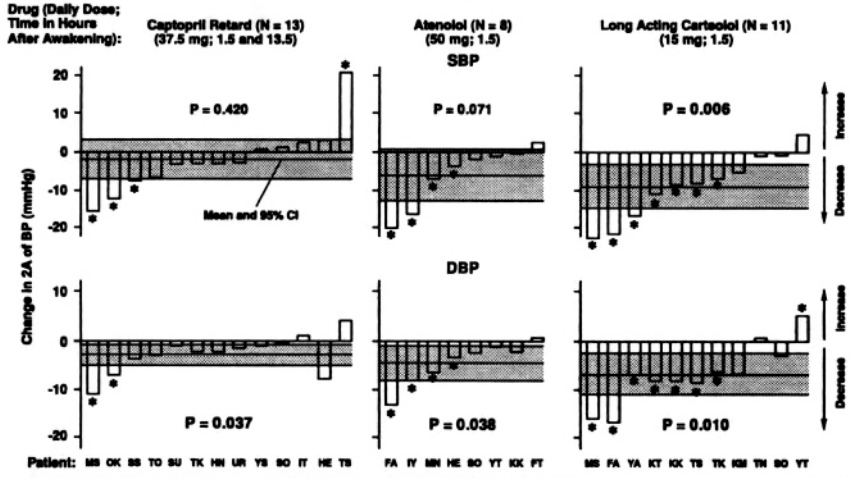
28990-01



CC 4/95

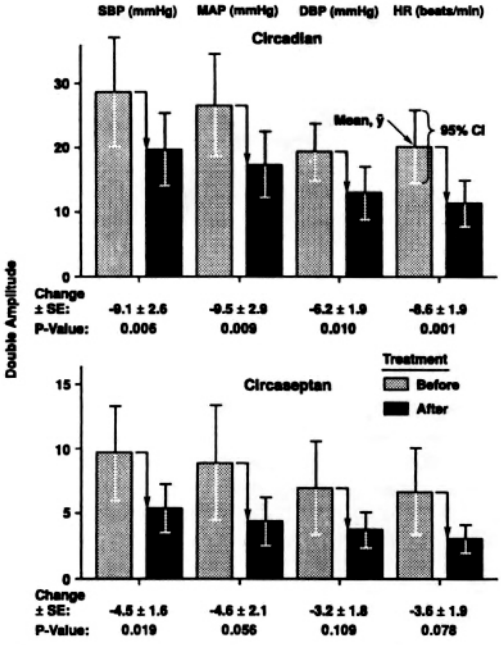
Fig. 18

LOWERING OF THE CIRCADIAN DOUBLE AMPLITUDE (2A) OF SYSTOLIC (S) AND DIASTOLIC (D) BLOOD PRESSURE (BP) IS A MATTER OF THE PATIENT AND DRUG DOSE (AND TIMING*)



* P < 0.05 from individual comparison (after vs. before treatment); timing effect shown elsewhere. CC 6/95

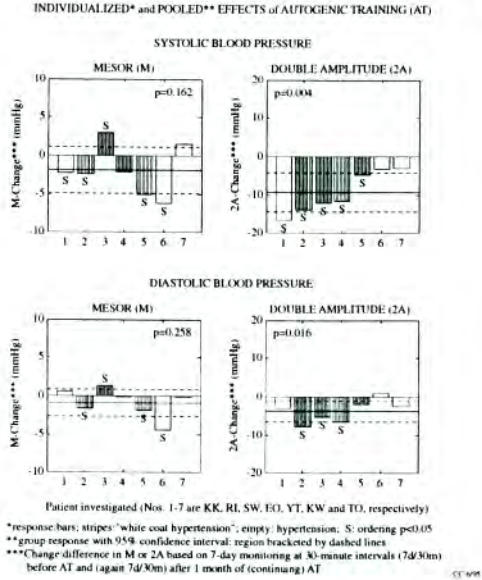
EFFECT OF LONG-ACTING CARTEOLOL (15 mg/day) ON TWO CHRONOME COMPONENTS OF SYSTOLIC (S), MEAN ARTERIAL (MA), DIASTOLIC (D) BLOOD PRESSURE (BP) AND HEART RATE (HR)*

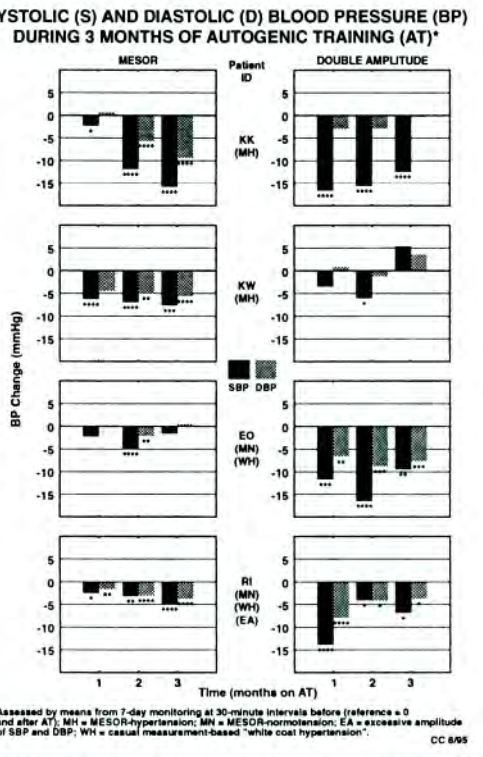


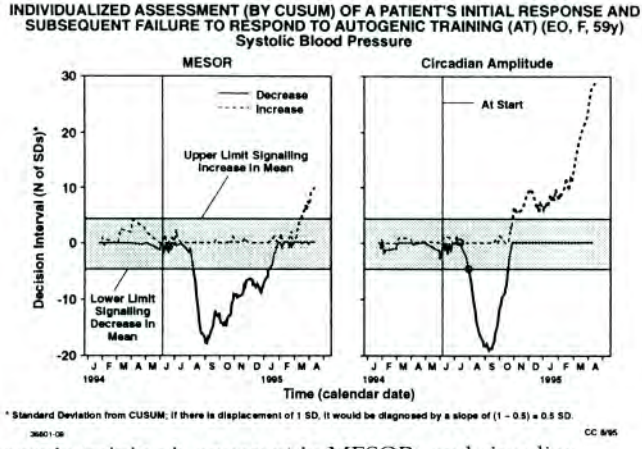
* Monitoring before and after treatment at 30-min intervals for 7 days of 11 patients. CC 6/95

The usefulness of a chronobiologic approach is supported by the demonstration that certain antihypertensive drugs can lower the circadian blood pressure amplitude. For instance, captopril retard and atenolol slightly reduce the circadian amplitude of diastolic blood pressure but not that of systolic blood pressure, whereas a long-acting formulation of carteolol reduces the circadian amplitude of both systolic and diastolic blood pressure (top). Numerically, the decrease in amplitude is larger for atenolol than for captopril and it is even larger for carteolol. Carteolol also reduces the circaseptan amplitude of blood pressure (left).

Findings of Y. Watanabe.



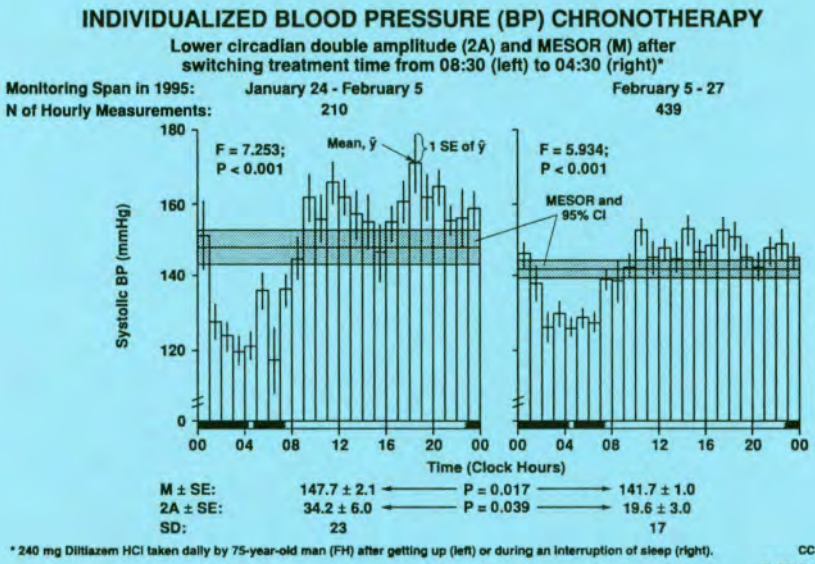


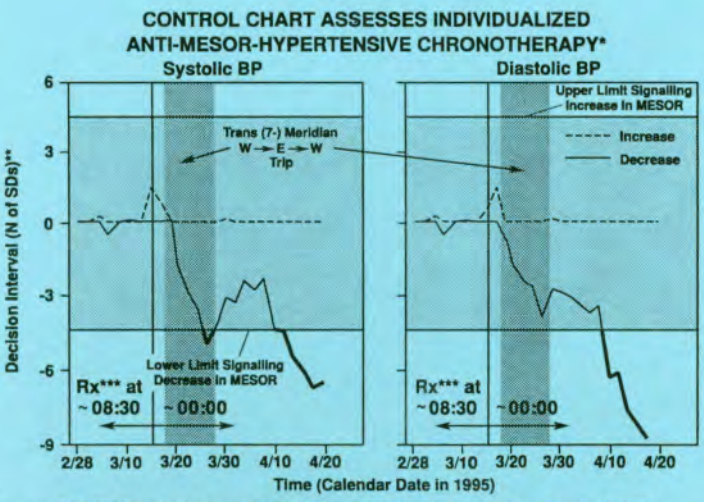


Autogenic training, a relaxation technique, can lower the circadian amplitude of blood pressure in some patients. After one month on autogenic training, the decrease in circadian blood pressure amplitude can be validated on a group basis (second column in top left figure). In 3 of 4 patients who continued monitoring their blood pressure, the decrease in circadian blood pressure amplitude persists (at least up to 3 months) and is accompanied by a usually small decrease in MESOR (first column in top right figure). Among the statistically significant effects, medical signification of the effect of autogenic training is apparent in MESORs and circadian amplitudes of patient KK alone. The initial lowering of MESOR and circadian amplitude seen for patient EO, documented by a self-starting cumulative sum (cusum) control chart, is lost at a time coincident with a load (conflict with neighbors) (bottom). Autogenic training may be a useful technique to reduce the circadian blood pressure amplitude of some normotensive patients with an excessive circadian blood pressure amplitude who are at a much higher risk for ischemic stroke and nephropathy (see Figures 10 and 11, pp. 30-31). It remains to be seen whether a reduction of the circadian blood pressure amplitude by pharmacologic or non-pharmacologic means can reduce the incidence of adverse vascular outcomes in patients with an excessive circadian blood pressure amplitude.

Findings of Y. Watanabe.

Chronotherapy to optimize treatment effects on MESOR and circadian amplitude of blood pressure





The usefulness of a chronobiologic approach is supported by the demonstration that treatment with antihypertensive drugs can be optimized by timing. The same dose of the same drug can have different effects on the MESOR and circadian amplitude of the same patient's blood pressure when it is administered daily at a different circadian stage as seen by the naked eye in top graph. The practicality of a chronobiologic approach lies in the availability of inferential statistical methods for the rigorous assessment of intervention effects applicable to the individual patient as shown in bottom graph.

IMPEACHMENT OF CASUAL BLOOD PRESSURE (BP) MEASUREMENTS AND THE FIXED LIMITS FOR THEIR INTERPRETATION *AND CHRONOBIOLOGIC RECOMMENDATIONS*

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Abstract prepared by invitation for the meeting in Ferrara, Italy, of the New York Academy of Sciences, September 10-12, 1995,
amplified by reference to a table and figures in this resolution, prepared with Patrick Delmore, Director of Communications, Medtronic Inc., Minneapolis, Minnesota (phone 612-574-3725; fax 612-574-4563), to whom requests for reprints may be addressed

The about 40% error in diagnosis associated with the current approach *to BP* likely stems 1) from reliance on one or a few readings taken in the physician's office when the within-hour standard deviation of BP is of the order of 7 mm Hg *[1]* and *the within-day change exceeds 50 mm Hg (Figures 1, 2 and 13)* and 2) from the interpretation of BP records in the light of fixed limits such as 140/90 mm Hg (systolic, S/diastolic, D BP) when built-in circadian and infradian rhythms of large amplitude (A) have been documented *(7). Fixed thresholds (best replaced by chronodesms) can render the office BP measurement equivalent to flipping a coin (Table 1 and Figure 14).* Estimating parametric *(Scheme 1)* (MESOR, A and acrophase of major anticipated rhythmic components and of their harmonics) and non-parametric (percent time elevation, hyperbaric index and timing of excess) endpoints, even for MESOR-normotensive patients, is desired in view of the association of an enlarged circadian BP-A with 1) familial antecedents of high BP and related vascular complications *[2];* 2) morphologic changes in the heart revealed by echocardiography *in adulthood [3] and also after the in utero exposure to betamimetics, observed in neonates [2] and in adolescence [4];* and 3) actual adverse outcomes *(Figures 9-11) (34).* A chronobiologic approach based on manual if not on automatic self-measurements is useful since certain behavioral interventions as well as certain antihypertensive agents, when given at the appropriate time, can lower the circadian (and circaseptan) BP-A *[5].* Its practicality lies in the availability of statistical methods, notably control charts based on self-starting cumulative sums for the **individualized** assessment of intervention effects *(Figures 16 and 17).* Longitudinal monitoring is needed so that 1) reference values from low-risk individuals become widely available; 2) the earliest rhythm alteration can be picked up early before there is target organ damage; 3) **timely intervention is instituted** when needed and is **targeted in time** *(Figure 12)* for highest efficacy with minimal side effects; and 4) infradian BP variability associated with psychophysiologic responses *(see inside back cover)* or with unusually prominent circannual variation *(Figure 5d)* is recognized. Reference values for circadian and infradian rhythm parameters require systematic longitudinal monitoring and software for the windowing, compacting and recycling of information *(Figure 18),* readily achieved for the experimental animal, yet still awaiting the design of unobtrusive monitoring instrumentation for use in the much larger human being.

Note: References on pp 8-10 in ( ); those below in [ ].

1. Cornélissen G.: Instrumentation and data analysis methods needed for blood pressure monitoring in chronobiology. In: Chronobiotechnology and Chronobiological Engineering, Scheving L.E., Halberg F., Ehret C.F. (eds.), Martinus Nijhoff, Dordrecht, The Netherlands, 1987, pp. 241-261.

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3. Kumagai Y., Shiga T., Sunaga K., Cornélissen G., Ebihara A., Halberg F. Usefulness of circadian amplitude of blood pressure in predicting hypertensive cardiac involvement. Chronobiologia 19: 43-58, 1992.

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5. Tamura K., Kohno I., Saito Y., Wakasugi K., Achiwa S., Imanishi Y., Cugini P., Halberg F. Antihypertensive individualized therapeutic strategy. Difesa Sociale 6: 109-124, 1991.