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Season's Appreciations 1998

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Our reference values are in the form of 7-day series of hourly or denser around-the-clock data for a minimum of a week, for both genders, from womb to tomb, for "whites"

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We thank all of those who have supported the continuance of chronobiology at the University of Minnesota. Special credit is due to Earl E. Bakken, who introduced the implantable cardiac pacemaker and also the concept of the free-running oscillator, an invaluable device and a fertile concept, respectively. Free-running led to the coining of "circa" rhythms. There may again be a center that does more than the design and/or analysis of work done elsewhere. We have started to try to bring into the mainstream of health care (Halberg F. 1998; Cornélissen et al. 1999) the fruits of an approach that led Erna and Julia (Halberg J. et al. 1980) to the documentation of a murine disease risk syndrome.

A very large circadian amplitude of blood pressure (Otsuka 1998) and a very small standard deviation of heart rate (Cornélissen et al. 1999) underlie asymptomatic clinical conditions of high disease risk. One of these risk syndromes is circadian blood pressure overswinging or CHAT, short for circadian hyper-amplitude-tension. Another syndrome, in health (!), is an excessively low variability in heart rate, called CAHRV, for chronome alteration of heart rate variability (Kleiger 1987; Cornélissen et al. 1990; Otsuka et al. 1997). The switch from focus on rehabilitation (after the fact of catastrophic disease) to the lowering of an elevated disease risk in the superficially healthy person—pre-habilitation—became our major concern in 1998, notably for stroke prevention. Locally and in a worldwide cooperation first and foremost, we monitored blood pressures, heart rates and electrocardiograms for spans of not less than 7 days whenever possible. Whenever indicated and for research, individuals monitored themselves for much longer durations.

We had the pleasure of cooperating along several lines with Kuniaki Otsuka (1998), who published a book on a chronocardiology sui generis. One of his 7-day monitorings on himself sufficed to detect a statistically significant lowering of variability in his R-R intervals during a magnetic storm: no effect was found at the 3.6- second power ($P>0.50$), associated by others with parasympathetic activity while a statistically highly significant effect was ascertained at 10.5-second power, in association perhaps with other aspects of the autonomic nervous system. While this is one case only, the overall reduction in heart rate variability was exactly what had earlier characterized the ECGs of eight cosmonauts during a magnetic storm in space vs. the ECGs of 41 cosmonauts in space during magnetically quiet conditions (Baevsky et al. 1997). A reduction in the circadian standard deviation was also found in people at high vascular disease risk (Cornélissen et al. 1990; Otsuka 1998). We continue to offer free BP monitoring to all comers. This has already led to the detection of CHAT, which appeared to be fulminant in a 35-year-old computer scientist. He did not heed our advice for added monitoring after an acceptable stress test but a few months later called us to ask for an implantable monitor. When asked what accounted for a change in his attitude toward monitoring, he informed us that he had had a myocardial infarction. The results of a prospective 6-year study on 297 patients and a follow-up publication on 424 patients had not convinced him. It took a personal event to prompt him to ask for a monitor and he wanted only an implantable one—a hint for industry.

Conceivably, in some cases, because we did not act for pre-habilitation in the absence of a need for rehabilitation, we lost a number of outstanding chronobiologists. This past summer, Juergen Aschoff did not accept our cordial invitation to Minnesota, where we could have monitored him, even if this may not have prevented the series of strokes that claimed his life. Along with Colin Pittendrigh, another prominent scholar of clocks, he had championed with a good intuition and scholarship what, deep down, is an inferential statistical science, i.e., what with much sweat and statistical validation we had dubbed nearly half a century ago as free-running, with advice from Earl Bakken. Both Aschoff and Pittendrigh share in the credit of popularizing circadian timing, which, in the interim, in the form of a built-in biological day, has spawned a plethora of approaches by molecular geneticists, while we could document the emergenic heritability on the heart rate of twins reared apart. We now also recognize, with the built-in biological week, month and year, further components in a rhythm spectrum. We are testing the extent to which the half-week, the week and the half-year are special signatures of helio-geomagnetics (Grafe 1958); the decade and the double decade are probably also built into our internal integrative (Halberg et al. 1990) as well as (Darwinian) adaptive time structure, but this, as yet, is speculation that is very difficult and time consuming to test. There is much accumulating evidence, suggesting that we still resonate with these spectral components of an invisible yet tangible helio- and geomagnetic master switch, complementing light and temperature (Halberg and Cornélissen 1998; Cornélissen et al. 1999).

Also in 1998, we bade farewell to Werner Menzel in his 90th year. He did all the right things for health care, many decades ago: he wrote an invaluable book (Menzel 1962) which remains a source of much useful information, notably in a historical context; he introduced a pump for drug delivery; and he sought quantification by fitting sinusoids to his data.

Arne Sollberger, who died in June, wrote a book in 1965 thoroughly reviewing what became chronobiology, and for a long time was the indefatigable secretary of the International Society for Biological Rhythms (now the International Society for Chronobiology).

Another friend, recent but staunch, whom we should have persuaded to undergo physiological monitoring was Boris A. Nikityuk. Boris was Professor and Head of the Department of Anatomy and Anthropology at the Russian Academy of Physical Education in Moscow, a Member-Correspondent of the Russian Academy of Medical Sciences (RAMS), and President-Founder of the International Academy of Integrative Anthropology. At the June 30, 1997 meeting of the RAMS on the BIOsphere and the COSmos (BIOCOS), where we met at a distance, Boris presented previously published data covering 112 years on the human newborn's height, weight, and the circumference of head, chest and abdomen, in order to suggest the effect of non-photic solar activity upon us. Based on a meta-analysis of his data and those of others, Elena Vasilievna Syutkina, chrononeonatologist par excellence with some of us, detected the signature of solar activity in neonatal morphology and physiology (Cornélissen et al. 1999).

Sunspots had been seen and reported by Galileo, Scheinert, Fabricius and Harriot at the beginning of the seventeenth century. These and other luminaries in physics, however, ignored cycles, until the pharmacist Samuel Heinrich Schwabe in 1843 recognized the importance of periodicity in the numbers of sunspots (Dictionary of Scientific Biography 1965). Boris Nikityuk shared our interest in the 10.5-year Schwabe cycle as the "first floor" of politics and economics as well as of biology. A wonderful friendship and nearly daily correspondence by e-mail culminated in our getting acquainted in Vinnitsa, Ukraine, in May 1998

at the II International Congress of his International Academy of Integrative Anthropology. On September 29, 1998, he retired to bed, and was found dead the following morning. He had suffered a massive stroke.

We honored both Boris and Werner by dedicating to them the proceedings of the 3rd International Symposium on Chronobiology and Chronomedicine in Kunming, China, on October 7, 1998 (Halberg and Cornélissen 1998). Those in attendance stood in silence for one minute to pay a very small tribute to the many contributions of their lifetimes. We also dedicated to Menzel's and Nikityuk's memory abstracts at the 6th Conference of the Italian Society for Chronobiology in Chianciano Terme (November 27-28) (Cornélissen et al. 1998, Halberg et al. 1998).

Old and new ties in China and Europe led to the coining of pre-habilitation and to laying the seeds for implementing it. In strategic positions in this context are Xue Zhennan, Jinyi Wu and Zhengrong Wang in Chengdu and Ziyan Zhao and Ziying Zhao in Jinan, all interested in a stroke prevention program. With Jarmila Siegelova, the new chair of pathophysiology in Brno, Czech Republic, with her colleagues Bohumil Fiser, the new head of physiology, and Jiri Dusek, we contributed to an international fair of medical technology and pharmacy. With Anatoly Delyukov and Yuri Gorgo of Taras Shevchenko University in Kiev, Ukraine, we learned of associations between atmospheric pressure perturbations and the human ECG. A cooperation also started with Lev Gheonjian and Tamar Paatashvili of the Abastumani Astrophysical Observatory in the Republic of Georgia. We initiated comparative studies of mortality from myocardial infarctions in two locations at similar geographic but different geomagnetic latitude. In Minnesota, we found an excess 220 deaths from myocardial infarctions per year during spans of high solar activity, as compared to years with low solar activity. Franca Carandente in Milan is in a key position in Italy, as was Brunetto Tarquini, Professor and Head of Internal Medicine at the University of Florence, the clinical leader in chronomedicine. Sadly, with this season's appreciations, we also bid farewell to Brunetto, the dearest of friends, who passed away on December 10, 1998. Brunetto was on the frontiers of endocrinology, documenting the chronobiology of leptin (Tarquini et al. 1999), dehydroepiandrosterone sulfate (Tarquini et al. 1997a), endothelin-1 (ET-1) (Tarquini et al. 1997b and c) and melatonin (Tarquini et al. 1997d). When many investigators focus on circadian clocks, he discovered an 8-hour ET-1 rhythm. It is to Manfred Herold's (1998) great credit to have shown that a circaoctohoran can coexist with a 24-hourly cortisol pattern in clinical health and that for ET-1 it can be prominent in the absence of a circadian component.

In memory of Brunetto, let us endeavor further to replace a single- sample medical art by the science of time series. Thereby, we pave the way for prehabilitation by monitoring for risk assessment, which prompts action as a main feature of the health sciences, serving to maintain what Earl Bakken (1998) calls the health-related quality of life.

This is what our publications are mostly about. The task on hand for chronobiologists is challenging, greater than that of Oliver Wendell Holmes, Joseph Lister and Ignaz Semmelweis. The Bostonian surgeons of Holmes' day, the Britons and Scots of Lister's and the Viennese of Semmelweis' continued to mock the notion that they must scrub before operating, and used their scalpels while wearing their street clothes (Sutcliffe and Duim 1992). Are we any less odd by recommending an initial 7-day blood pressure and heart rate profile, and a much longer surveillance of blood pressure when necessary, as is often the case for a lifetime, as long as we have no real cure for a deviant pressure?

To realize our handicaps, we cite the following facts from our Minnesota backyard:

+ One of the best internists in our area, a former student who spent evenings and weekends as a volunteer in our laboratory, scrutinizing the evidence on CHAT—a co-author of a report on that topic—did not encourage self-measurements by a friend, his patient, because he "could do nothing" about spikes in pressure, evidence to the contrary notwithstanding (Halberg and Cornélissen 1995; Watanabe et al. 1996a and b).

+ Another co-author, also of a paper on blood pressure monitoring—who as a top administrator had defended our science vigorously and wholeheartedly—could not suppress softly, and perhaps reluctantly saying "hyperbole" when we equated a 24-hour profile of blood pressure in some cases to flipping a coin; yet this same figure was endorsed by an international resolution as well as by data (Halberg and Cornélissen 1995).

+ Other scholars make great contributions to chronobiologic research, yet for them an integration of chronomes in as with those around us remains as esoteric as free-running circadians were half a century ago, when they were called locally "Halberg's paranoia."

Honi soit qui mal y pense: All these outstanding individuals are invaluable to a budding chronobiology. Nonetheless, chronomedicine will remain a wallflower unless we recognize that our time structures, resolved as chronomes, are the foundation of a scientific approach to health care. For this discipline to

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enter the mainstream, it must be more than a complement, used mainly for research. Instead, chronobiology is the scientific alternative to the art of health care of our day. There is no other justifiable alternative to lower cost while improving quality (Halberg et al. 1993), but there are several indispensable complementary approaches. The best approach, empirically validated by everybody who practices health care as a profession rather than an occupation, is a good, invaluable "bedside manner" and empathy: what Earl Bakken calls "high touch." Some other complementary health care practices as yet need to be tested. In many cases we confront subtle effects, including the effects of placebos (Stunkard 1950; Charlton 1995; Linde et al. 1997; Brown 1998; Bunk 1998; Viza 1996, 1998; "When the Blind is Broken" 1998), occurring mostly within the normal range. Chronobiology is the most sensitive way to gauge any benefit.

Chronobiology may be labelled as "too time-consuming," "too complicated" and/or "too expensive." Learning to read and write is also time-consuming, complicated and expensive. The concept of universal literacy originally met with opposition from those who felt that if everyone could read, no one would be willing to do menial tasks for little (or no) pay. To paraphrase the observation of Joel Chandler Harris' character Uncle Remus, if you put a spelling book in a slave's hands, right then and there you lose a plowhand (Zinn 1990).

In a recent report in the St. Paul Pioneer Press (Majeski 1998), a cardiologist teaming with us in a blood pressure and compliance study claims that "...Halberg minimizes the difficulty of wearing an automatic monitor for seven days because 'he has very devoted subjects'." (One of those subjects, the mayor of the suburb where some of us live, wrote to us and denied he was that devoted!) The population at large, via its political leaders such as this mayor, must be convinced that just as a literate person no longer needs to rely on scribes to write letters, so is there no longer a need to take "the" blood pressure at the clinic. There is no need for a 24-hour profile, notably when it is not interpreted chronobiologically, but it can cost $200 for a single 24-hour span. Once a system is developed, as we are attempting to do in Minnesota, the initial 7-day monitoring can become routine. Interested persons should contact us (Germaine Cornélissen: e-mail: **corne001@maroon.tc.umn.edu**; phone [612] 624-6976; fax [612] 624-9989. Until further notice, available user-friendly portable blood pressure monitors make it possible for anyone in our locale at this time to do monitoring for 7 days or for longer spans when needed. The indispensable wherewithal for the analysis of the data is available in our laboratory, as a start as a public service. Our reference values are in the form of 7-day series of hourly or denser around-the-clock data for a minimum of a week, for both genders, from womb to tomb, for "whites" and "Asians."

Paraphrasing an academic engineer (Duechting 1998), breakthroughs in health care depend upon the following items:

1. the vision of a leader, 2. the creativity of staff, 3. a friendly work environment, 4. an appropriate technology, 5. an auspicious start time and 6. the adherence to a time line. Indeed, we may not deal with the sum of these ingredients, but with their product.

+ Regarding Item 5, to bring chronobiology into the mainstream, any time is not only auspicious, but overdue, notably if we are sidetracked by unexpected findings prompting our return to excursions into the cosmos (Halberg and Cornélissen 1998; Cornélissen et al. 1999; cf. Halberg 1961, 1964a and b; Halberg et al. 1970). Here, adverse effects characterizing rhythmic, and to that extent predictable, solar-terrestrial and broader interactions with human pathology as well as morphology and physiology can lead to useful results on terra firma as well. Findings made warrant prospectively refined archival studies of human morbidity and mortality in geomagnetically and geographically differing areas and in space (Halberg and Cornélissen 1998). Results also warrant strategically placed worldwide and extraterrestrial systematic monitoring. The ECG, or at least heart rate, and blood pressure and as-yet opportunistic metabolic, neural and endocrine studies should become systematic. The biological approach will have to be coordinated with physical monitoring to pick up disease risk syndromes and to develop countermeasures for instrumented self-help for risk reduction in health care. Such pre-habilitation is deemed essential in extraterrestrial space, away from hospitals. Longitudinal monitoring for a lifetime of different non-human species and hybrid (combined longitudinal and transverse) monitoring of humans can provide hints of the sites of life's origins and evolution(s).

Putative effects of magnetic field disturbance upon mortality on earth were found neither by others (Lipa et al. 1976) nor by ourselves, when in 1998 we examined overall mortality from all causes in Minnesota in relation to Schwabe's about 10.5-yearly (circadecennian) cycle in solar activity (Cornélissen and Halberg, unpublished). This was at variance with long-held claims of magnetic storm effects by Russian (Chizhevsky 1940, 1968; Dubrov 1978; Breus et al. 1989) and other investigators (Düll and Düll 1934, 1935), including subtle geophysical effects reported by prominent physiologists in the U.S. (Brown 1960; Barnwell 1960). Dr. Tamara Breus, however, had given one of us skeptics an opportunity for a chrono-

meta-analysis of a data set of over 6,300,000 diagnoses made in response to calls for an ambulance in Moscow during three years of high solar activity (1979-1981) (Breus et al. 1989). With a variety of approaches, ranging from cross-spectral coherence to superimposed epochs, an effect of magnetic storms could be validated on 85,819 cases of myocardial infarctions (Halberg et al. 1991; cf. Halberg et al. 1992; Cornélissen et al. 1993, 1994; Breus et al. 1995), among other effects of interest to space life science (Halberg et al. 1991).

These results were subsequently confirmed by a different method which removed rhythms before the analysis of the heliogeophysical effect and were then extended to an effect of storms upon strokes and to another data set (Villoresi et al. 1994a,b; cf also Feigin 1997). An effect of magnetic storms was also reported for traffic accidents (Strestik and Prigancova 1986). Why earlier claims, thoroughly reviewed by Dubrov (1978) and Gamburtsev et al. (1994), could not be consistently documented, may have a complex answer, and more than insufficient sample sizes may be involved, although Tamara's over 6 million cases helped. As one of many pertinent considerations, the solar cycle number and stage may lead to quite different associations (Cornélissen et al. 1998; Halberg and Cornélissen 1998; Halberg et al. 1998; Nikityuk et al. 1998; Sothern et al. 1998; Watanabe et al. 1998). Thus, when a series of automatic half-hourly around-the-clock measurements of heart rate covering 11 years is correlated with the Wolf numbers (WN), there is a statistically significant positive correlation during the ascending ($r=0.535$; $P=0.001$), but not during the descending stage ($r=0.078$; $P=0.556$) (Watanabe et al. 1998). For another series covering 30 years by up to 6 measurements/day, heart rate was positively correlated with WN during the descending stage of one solar cycle (Jan 1970-Dec 1975: $r=0.398$; $P=0.001$) and negatively during the next 2 descending stages (Jan 1982–Dec 1985: $r=-0.427$; $P=0.002$, and Aug 1991–Jul 1996: $r=-0.450$; $P<0.001$). A remove-and-replace approach also revealed solar effects upon the amplitude of about 7-day cycles in heart rate (Cornélissen et al. 1996).

Concurrently, a chronobiologic approach can be suggested with respect to the origins and development of life. The study of the timing of circadian rhythms in nucleic acids was a first hint of an RNA world before ours based on DNA (Halberg et al. 1958, 1959; Barnum et al. 1958; Edmunds and Halberg 1981). By 1991 (Halberg et al. 1991; cf. Cornélissen and Halberg 1994; Breus et al. 1995), ontogeny (regarding, e.g., newborns as living fossils) and phylogeny were considered clues to the physical setting in which life came into existence. (Halberg et al. 1990; Cornélissen and Halberg 1994; Diez-Noguera et al. 1996; Thaela et al. 1997; Fanjul-Moles et al. 1998; cf also Halberg and Conner 1961; Schweiger et al. 1986; Woolum et al. 1998). A recapitulation, along the lines of the coiner of ecology (Haeckel 1905), originally Haeckel's Biogenetic Law ("ontogeny recapitulates phylogeny"), much disputed (de Beer 1930; Gould 1977; Alberch 1980; Bonner 1982; McNamara 1982; Halberg et al. 1990, 1998; McKinney & McNamara 1991; Goldbeter 1996; Halberg 1997), has evolved into an evolution of ontogeny discussed by scholars of heterochrony, mostly in terms of morphological characteristics. We in turn have sought the lessons yet to be learned about the evolution of rhythms from their development from the egg, as also advocated subsequently in principle by Prigogine (in the introduction to Goldbeter 1996). These evolutionary topics could all be approached empirically by systematic coordinated physical and physiological monitoring, i.e., by what developed into an agenda for BIOCOS, presented at a meeting at the International Union of Physiological Sciences, endorsed by the Russian Academy of Medical Sciences (Halberg et al. 1998) and proceeding on back burners, to be implemented on an appropriate scale.

+ About Item 3, the work environment is ideal; it is the world at large, motivating a small team, cooperating with quite a few local and many other friends, most of them apparent from the bibliography. Elsewhere, one of us (Halberg 1963) indicated that productivity is inversely proportional to the funds at one's disposal. By that criterion, we should be most productive. We are not distracted, but stimulated to derive more fun from our findings.

+ With respect to Item 2, our creativity must be judged by the reader of our bibliographies.

A U.S. physicist, former coordinator of the International Solar-Terrestrial Energy Program, interested in breaking down disciplinary barriers (Roederer 1985), wanted to initiate a Solar Activity and the Biosphere (SABIO) project. We cite him verbatim (Roederer 1995): "If confirmed, the implications of solar variability-induced effects of biota and human health, however small, could be far-reaching. Leaving aside the potential impact on preventive medicine, health care and insurance, they would be of basic importance to chronobiology." We add that chronobiology could spawn two budding fields that depend upon coordinated physical and biological monitoring, notably on humans: chronoastrobiology and, to those astronauts who explore space, chronobioastronautics. The extension of the data for learning more about our origins and for venturing further is the task of BIOCOS. This may be the road leading to the next item:

+ Regarding Item 4, the appropriate technology for closing the loop between available diagnostic and

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therapeutic devices is desirable for a mainstream chronomedicine (Cornélissen et al. 1999). Interest by both the public and private sectors will be essential to transfer the monitoring technology, now sufficiently miniaturized from mice to human beings.

+ Item 6 is a problem. We are general practitioners of chronomedicine, tackling whatever problem comes our way, and are not good in adhering to timelines, except for being at it 7 days a week for many hours each day.

+ For Item 1, we are fortunate to have Earl E. Bakken as the mentor of a future center. He has already made the implantable pacemaker into a reality. This invaluable device in health care is a *sine qua non* for *the rehabilitation* of many of the sick. Earl also had an early encounter with what developed into chronobiology and may now help this established discipline to reach the mainstream. His vision, implementable by chronomedicine, is action to improve the health-related quality of life (Bakken 1998). Earl advocates the use of multiple modalities ranging, as he puts it, from high touch to high tech, from bedside manner and placebo effects of use to the patient in their own right to the action of externally provided molecules and devices. Most, if not all, treatments have or should have some ingredients from high touch and more and more treatments will involve high tech as engineering becomes chronobiomimetic.

High touch effects can gain greatly from the monitoring and other methods of chronomedicine, which provide entry into the otherwise-ignored normal range, and thus seek to pick up subtle effects. Earl has a vision, which we share, of making integrated health care into a chronomedical reality. Our name for the road to the realization of this vision is prehabilitation. The Minnesota center in chronomedicine has as its goal to assure that the benefit from splitting the normal range of variation will not take another hundred years! The center's focus is directed at a scenario eloquently described elsewhere in a different context (Whitaker 1998):

You're a vibrant 52-year-old executive, avid tennis player, loving husband and father. Then, in an instant, a stroke irrevocably tears apart the entire fabric of your life. You now can't walk without assistance. Your left arm is crippled and your speech is slurred. When your friends and business associates come to visit you, they can hardly believe it's you. You are a shadow of your former self, unable to work, walk without great difficulty or even carry on a conversation. You must drag yourself up stairs. And you face what seems like an eternity of gruelling therapy to merely regain a fraction of your lost function. Now let me ask you a question—If you could avoid this by taking a few simple precautions, wouldn't you do it? [Stroke] strikes half a million Americans [and, we add, many more around the world] every year, killing 150,000 people, 20% within the first month. Depressingly, only 10% of people who have a stroke ever resume completely normal function.

The chronobiologist asks: If you could avoid a stroke, which in the worst massive case may even leave you unable to clean, feed, dress or otherwise care for yourself, by investing into a week of somewhat obtrusive monitoring, along with other simple precautions, wouldn't it be worth it? The chronomedical initiative is to motivate the public and the health care provider, in this order of priority, to focus on the concept of pre-habilitation, not only with respect to stroke and to other vascular conditions, but with attention paid to all possible risks, so that the person saved from a stroke does not end up with another crippling or painful disease. The chronobiology center will accordingly focus on disease risk syndromes and thereby will strive to achieve the change in health care from after-the-fact endeavors to the detection of elevated disease risk and its lowering by treatment, pre-habilitation.

The reduction of too much variability in blood pressure and the augmentation of too little heart rate variability will be the major immediate goals. We will focus on circadian blood pressure overswinging or **CHAT**, short for **c**ircadian **h**yper**a**mplitude**t**ension, and upon an excessively low standard deviation of heart rate, a **CAHRV**, a **c**hronome **a**lteration of **h**eart **r**ate **v**ariability. For the purpose of diagnosing these conditions, the availability of reference values from peers of both genders, all ages and different ethnic groups, eventually with outcomes, will be critical. For this purpose first and foremost, the data store accumulated over the past 50 years must be organized while at the same time invaluable accumulating records of much broader scope are to be catalogued and archived. Equally important is the continuance and systematic extension of the collection of time-specified reference values around the world from womb-to-tomb. This is under way in the context of the ongoing projects on the **Bio**sphere and the **Cos**mos (BIOCOS). This endeavor gained momentum from Dr. Kuniaki Otsuka's now international, originally **A**sian **C**hronome **E**cologic **S**tudy of **H**eart **R**ate **V**ariability (ACEHRV).

These ongoing projects provide invaluable reference standards for blood pressure, heart rate and other ECG indices, some derived from beat-to-beat 7-day or, when need be, longer ECG records. Invaluable data may continue to accumulate cost-free due to our function as a design and data analysis center. By such planning and analytical endeavors, the center is

likely to have further opportunities to bring chronobiology into the mainstream of health care. Its goals include the collection and organization of data on the variability of indices of risks competing with vascular disease risk. Endocrine gauges of cancer and emotional disease risk have been the result of coordinated international studies (Halberg et al. 1981). In the course of these endeavors, major focus will also be placed, whenever possible opportunistically, on the underlying mechanisms that may lead to new treatment modalities, involving physical approaches, such as the manipulation of electricity and magnetism.

We will be available to test new technology aimed at closing the loop between available and yet-to-be-developed diagnostic and treatment devices with a view of their use where they are most needed such as in missions in space where neglect of the limits to acceptable blood pressure and heart rate variability may have consequences such as those of the neglect of limits of O-rings to acceptable temperatures, leading to the Challenger disaster (Feynman 1988). Focus upon this dividend from chronoastrobiology could provide both a model for health care on earth and also basic data on the origins of life, an intellectual dividend for center staff (Dorman et al. 1993; Doarn et al. 1998).

The bottom line of our endeavors, the detection and treatment of disease risk syndromes, notably stroke prevention, is to be implemented locally as well as by as many as possible in a network of about 100 co-investigators worldwide. The first line of treatment for stroke prevention will be timed relaxation methodology (Watanabe et al. 1996a, b) to be applied before drug treatment. For this purpose and more broadly, chronobiologic self-help in health care, including family- and self-monitoring of vital signs, is to be taught and implemented as far as possible. This educational endeavor of the local public in different age groups will also constitute a major goal of the new center.

We thank Dana Johnson and his committee, Phil Regal and Dave Hunter in particular, for batting for a chronobiology center at the University of Minnesota. We appreciate the guidance to pertinent literature offered by Howard Burchell and again by Earl Bakken.With Salvador Sanchez de la Peña, the associate editor, we thank the editor-in-chief, the cardiologist Mircea Dumitru of Geronto-Geriatrics, for a Chronome-Geriatrics, and look forward to meeting Mircea in person. We also look forward to meeting Dr. Michael Fossel (1998), editor-in-chief of the Journal of Anti-Aging Medicine, whose enthusiasm, for which we are grateful, exceeds ours: in introducing our paper on CHAT he wrote a special note, paraphrasing our presentation by saying that we recommend to "avoid flying blind" in dealing with blood pressure and, we add, with any other variable.

Whether or not our plans are realized in Minnesota, we thank all of our past, present and future teachers (= editors = co-authors = referees = students = readers, in particular), who may help others and us to avoid flying blind, so that every day in 1999 and in the new millennium may be for them a chronobiologically qualified holiday.

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