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Circasemicentennial
Season's Appreciations

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In 1999, the Chronobiology Laboratories at the University of Minnesota continued their activities, with renewed focus on the Stroke Prevention and BIOCOS (BIOsphere and the COSmos) projects.

Earl E. Bakken

Pacemaker

For chronobiology, a new status and a new home

The Chronobiology Laboratories this year became a formal Chronobiology Center, thanks to a committee of peers headed by Dana Johnson, Professor of Pediatrics and Head of the Division of Neonatology at the University of Minnesota, advocating, beyond its continuance, the penetration of this discipline into everyday teaching and practice of health care as well as biology, a goal shared with Earl E. Bakken, builder of the first implantable cardiac pacemakers for long-term use. By this feat and others (see below), Earl is the chronocardiologist *par excellence.* As "Mr. High Tech," Earl is engaged in joining instrumented health care to "high-touch" concern for the individual's needs by establishing projects in leading institutions around the country. Activities in chronobiology centers around the world, coordinated in Minnesota, reported herein, are contributions regularly reviewed with him.

Our findings, reflected in the titles of publications following this report, were in part reported orally in Brno, Czech Republic, at a special symposium organized by Dr. Jarmila Siegelova (Professor of Rehabilitative Medicine, Masaryk University, Brno), opened by one of us, in celebration of the 80th anniversary of the founding of Masaryk University in Brno. Important findings were reported by others on the occasion of a symposium in July 1999, in celebration of the eightieth birthday of one of us, which coincided with the fiftieth anniversary of chronobiology at the University of Minnesota. A summary can be found at our website, **http://revilla.mac.cie.uva.es/chrono**. Our thanks are addressed to all those who wrote to reminisce; their thoughts have been posted on our website.

At this celebration, among many other fine presentations, data on four kinds of cancer cells grown in vitro, exhibited nearly sinusoidal, extremely regular, about-7-day rhythms. New experience was gained, old friendships renewed, and new ones established. We extend our appreciation to Frank Cerra, Senior Vice-President, Academic Health Center; Leo Furcht, Professor and Head, Department of Laboratory Medicine and Chronobiology; Susan Dunlop, Development Officer, Minnesota Medical Foundation; Charles Moldow, Associate Dean, School of Medicine; Neal Gault, Professor of Medicine emeritus; and in particular Cherie Perlmutter, Associate Vice-President, Health Sciences Administration, for their support of chronobiology expressed at the symposium. Our thanks also go to Minnesota Governor Jesse Ventura, who presented Franz with a certificate in recognition of 50 years of Minnesota chronobiology, and to Dan Wall, Mayor of Roseville, Minnesota, who described his experience in blood pressure monitoring as a father, concern as a citizen and opportunity as a public servant, to make such monitoring available to the community as a whole, inspiring him to initiate the Roseville citywide blood pressure project.

Special thanks are here expressed to those who travelled from Japan, Europe and other parts of the U.S. to attend the Minnesota symposium. We learned from lectures by Franklin Barnwell, Christopher Bingham, Brian Brockway, Erhard Haus, Dana Johnson and Philip Regal, longtime associates of our laboratory. Renewed contact with Gabriel Fernandes of San Antonio, Texas; Dora K. Hayes and William Hambley of Fairfax, Virginia; William Hrushesky and Patricia Wood of Albany, New York; Marilyn Kosmala, originally from Chicago but now residing in the Twin Cities area; and Edmond Yunis of Boston were greatly enjoyed and led to projects for new joint endeavors. We particularly appreciated seeing "old family members": Leopoldo Garcia Alonso, now Associate Professor of Pediatrics at t he University of Santiago de Compostela and Chief of Pediatric Gastroenterology and Nutrition at the Hospital Materno-Infantil "Teresa Herrera" in La Coruña, Spain; Miguel Revilla of the Department of Applied Mathematics and Computer Science at the University of Valladolid, Spain, who deserves the credit for our website **(http://revilla.mac.cie.uva.es/chrono)**, and for making software for chronobiological analysis available on the web; Salvador Sánchez de la Peña, now director of the Seccion de Cronomedicina de la Unidad de Investigacion Medica de Enfermedades Metabolicas del Hospital de Especialidades del Centro Medico Nacional Siglo XXI del Instituto Mexicano del Seguro Social in Mexico City; Kohji Tamura, Professor and Head of Medicine and Cardiology in the 2nd Department of Medicine at Yamanashi Medical University in Yamanashi, Japan, with whom we enjoyed vivid discussions on "dipping and swinging"; Waldemar Ulmer, now with Varian International in Zug, Switzerland, who has undertaken the task of modeling feedsidewards from the viewpoint of theoretical physics, and whose outstanding experiments on cancer cells grown in vitro demonstrating prominent circaseptans were a highlight of the symposium; and Douglas Wilson of ADAS Cardiff in Cardiff, Wales, UK.

Foremost, it was a real pleasure to have not only the professional, but also the personal family together at the venue in Minneapolis. Francine and her husband Terry Kessler were able to stay for a week, a time used to its fullest to enjoy quiet family gatherings, parties with friends and colleagues, and other occasions for exciting discussions about diverse chronobiological topics.

The symposium coincided in time with our move from Lyon Laboratories, chronobiology's Minnesota home for nearly half a century, to a new center on the seventh floor of the Mayo Building (the former University of Minnesota Hospital), while the now-empty Lyon Labs lot will eventually house a Molecular Science building. In the negotiations leading to the creation of the center, Susan Dunlop of the Minnesota Medical Foundation played a critical role with much tact. Sally Palm of the Department of Laboratory Medicine and Pathology at the University of Minnesota, in innumerable ways, great and small, has helped to ease the move into our new quarters. We take this opportunity to express our indebtedness to both of them.

For the past fifty years, our focus has been on circa-rhythms, emphasizing the genetics of built-in cycles. We started with a study of inbred mice, reinterpreting as endogenous, with periodogram analyses, the free-running of mice[1] and then of humans, for the cases of about 24-hour and then of about-weekly and about-yearly rhythms. Lessons from the monitoring of twins reared apart about the role of genetics are now explored by many others at the molecular level. During this same past half-century, the spectrum of many organisms' rhythms was aligned with corresponding frequencies in the environment, that may account for how rhythms got into the genome in the first place.

The finding of a free-running about 7-day rhythm had prompted the search for an about 7-day component in geophysics, now confirmed by physicists, in addition to an anthropogenic, precise 7-day compo-

[1] The term "free-running," by analogy to the behavior of a self-sustaining oscillator and as a concept for biomedicine, was proposed by Earl Bakken.

nent in magnetic disturbance. The half-yearly component noted by geophysicists, notably Armin Grafe of Niemegk, Germany, led to the recognition that in human status epilepticus, there was no yearly component, but a strong half-yearly feature in the distribution of more than 50,000 cases prompting a call for an ambulance.

Prominent basic findings this past year revolved around numerical near-equivalents of the 10.5- and 21-year cycles in a variety of physiological and pathological as well as morphological variables. A hormonal change in the excretion of urinary 17-ketosteroids showed this circadecennian cycle, as did heart rate variability and mortality from myocardial infarctions in Minnesota, peaking shortly after the time of maximal solar activity. A cascade of these and related findings makes physiological sense insofar as the trough of heart rate variability preceded the circadecennian peak in mortality from myocardial infarctions, and in the same cluster of circadecennians were turning points of probable genetic changes in bacteria that may also contribute to the etiology of heart attacks.

These findings were reported by one of us in posters at the 22nd General Assembly of the International Union of Geodesy and Geophysics (Birmingham, UK, July 19-30) and at the 1999 conference of the American Geophysical Union (San Francisco, December 15). They were also presented in part in invited lectures at the 4th Congress of the International Society of Neuroimmunomodulation (Lugano, Switzerland, September 29-October 2), and at the Serono USA International Symposium on the Endocrinology of Aging (Tempe, Arizona, October 27-30). By contrast to a symposium in Washington DC in 1964 on "Stress in the Military Climate," where chronobiology was the opening theme, as it was in Tempe, any temporal considerations may have appeared as curiosities in Lugano. A notable exception was the contribution by Georges Maestroni, one of the organizers. Immunomodulation is precisely the field where timing can make the difference between speeding up a cancerous growth and inhibiting it, with the total dose/week being the same.

The meeting in Lugano was a welcome occasion to personally meet new friends, Peter G. Fedor-Freybergh, familiarly known as Gaudi, editor-in-chief, of both Neuroendocrinology Letters and the International Journal of Prenatal and Perinatal Psychology and Medicine and his partner Lili Maas, art director of the Neuroendocrinonogy Letters. A staunch friendship had already developed with Gaudi and Lili, fostered by numerous e-mail exchanges, following the submission of a manuscript by the late Brunetto Tarquini, presented last year in Blaubeuren, Germany, at a meeting organized by Christian and Hella Bartsch.

The chronome concept was recognized at the Serono Symposium, where the links between rhythms, chaos and age and other trends were emphasized as chronomes. Pertinent to the concept, insofar as it suggests a link between developmental changes and the circadian system, is work carried out independently by Dr. Ann Rougvie of this University and her graduate students on the roundworm *Caenorhabditis elegans*. It will be important to explore their basic contribution in clinical terms.

The chronome of heart rate was broadened earlier by inclusion of focus upon the correlation dimension and complexity in Kuniaki Otsuka's originally Asian, and now International Chronome Ecologic Study of Heart Rate Variability, that has been extended from where he started it in Japan, to China, India, Italy, Norway (Alta, above the Arctic Circle), Ukraine, and Michigan as well as Minnesota, USA.

The three-pronged human chronome approach, focusing on chaos, rhythms and trends, depends very heavily on long-term monitoring, which in turn allows resolution in heart rate and other variability of changes also along the scale of years. Along the latter scale, many sources of error are eliminated while new perspectives are gained by the discovery of circadecennians. As to error, several years of daily data on human 17-ketosteroid excretion are compatible with the assumption of a declining androgenic function, whereas subsequent years show an increase rather than a continued decrease, both opposite effects now being predictable parts of a circadecennian cycle. Unobtrusive automatic monitoring is the key of a new chronomedicine within the physiological range, which can then separate any trend with age from those with disease risk elevation.

The Roseville blood pressure project

In ancient times, people who needed a letter written but were not able to read or write themselves went to a professional scribe. When the Puritans of seventeenth- and eighteenth-century England began promoting universal literacy in the hope that it would make the Scriptures accessible to the masses, the aristocracy feared that widespread literacy would render the poor less willing to earn their keep through heavy and unpleasant labor. Today, universal education is the norm in most countries that pay at least lip service to the ideals of democracy and in most technologically advanced societies.

Similarly today, many in medicine feel that monitoring of vital signs such as blood pressure is best performed, and the data so gathered best interpreted, by trained health care professionals. But just as it takes time to learn to read and write, so also can the population at large learn to monitor their blood pressure with available automatic devices, so that on the basis of the data thus collected, informed decisions can be made. Personal blood pressure monitors are becoming as readily available today as were pens, pencils, typewriters and personal computers in years past.

Among disease risk syndromes, major focus was placed in 1999 on the fact that affordable devices have become reasonably generally available. A major effort was placed on the study of blood pressure overswinging, which can all occur within the physiological range of variation, just as heart rate underswinging, or circulating melatonin overswinging, can also occur with no deviation in mean value. The stroke prevention endeavor was welcomed by Earl Bakken, by far our center's staunchest supporter, and implemented by Dan Wall, the mayor of Roseville (a St. Paul suburb with a population of about 34,000), by his offer to each resident of Roseville of the opportunity to automatically measure his/her blood pressure and heart rate around the clock for seven days with an ambulatory monitor. For many, this length of monitoring seems overly long. In fact monitoring before the patient is seen by the physician was recommended by T.C. Janeway as far back as 1904, a lesson long forgotten. For others, including outstanding opinion-leading physicians, a week is not enough: they measured to the end of their lives, and some of our contemporary colleagues intend to do the same. For those who find 7 days too long for screening, we offer the following examples:

• For six days Mayor Wall's blood pressure record was perfectly acceptable, but he experienced one day of blood pressure overswinging (**c**ircadian **h**yper-**a**mplitude-**t**ension, or CHAT) while he kept score on a computer in a youth ice hockey game in which his son was playing. He had difficulty keeping track of penalty minutes, and some of the players, who were strong and contentious, did not hesitate to let him know that they were unhappy with his officiating outside his primary fields of law and government.

• A former head of cardiology at the Mayo Clinic—our mentor of long standing and the former editor of an important cardiology journal—had two initial days of blood pressure recording that were abnormally high, but thereafter his pressure was acceptable by chronobiologic criteria, that is in relation to the data from healthy age-matched peers of the same gender and ethnicity.

• A woman in Roseville had five consecutive days of deviant blood pressure, and thereafter an acceptable record for several months.

• Of 12 patients who were recalled after 7 years and who had originally monitored their blood pressure around the clock for a total of 9 days, only those two who had consistent abnormality had an event like myocardial infarction or had been found to need coronary artery bypass surgery.

The conclusion from these anecdotal cases and from studies on their trends are that for the given person, 7 days is a modest start and longer monitoring may be needed to avoid stroke, myocardial infarction, kidney disease and certain kinds of blindness.

The City of Roseville is working with the Chronobiology Center to offer monitoring to all citizens, from adolescents to old age. In some people, high blood pressures occur at night rather than during the day, spontaneously or presumably because of long-acting blood pressure-lowering medications that cease acting earlier than anticipated. These high blood pressures will not be recognized in measurements taken only during the day. It will also be possible to detect other deviant patterns that are indicative of an elevated cardiovascular disease risk, like a larger-than-usual change in blood pressure, called CHAT (short for **c**ircadian **h**yper-**a**mplitude-**t**ension), which usually precedes an overall elevation in blood pressure.

Visitors

We had the pleasure of hosting many visitors in 1999. Many of these individuals had come to participate in the Minnesota octogenarian symposium, while others chose to come at quieter times.

In November, Hugh Simpson of the University of Glasgow visited for two weeks, during which time we had many discussions concerning a chronobiologic brassiere for early detection of breast cancer risk, as yet available only for clinical use and as a prototype. Hugh's visit enabled the chrono-meta-analysis of findings Hugh had made and published earlier. The possible use of a bra studded with thermometric sensors for the long-term monitoring of breast surface temperature may serve for detecting changes that mammography cannot detect. Moreover, the thermometric bra may become applicable at ages when mammography is contraindicated. In the course of these reanalyses, Germaine made the incidental finding that the greater the number of live births a woman has, the greater is the circatrigintan thermal amplitude of her breast surface temperature, as if pregnancies reverse a trend in breast cancer risk. This finding suggests the possible use of a thermometric bra in scrutinies of the etiopathogenesis of breast cancer.

Keiko Uezono of the Institute of Health Science at Kyushu University in Fukuoka, Japan, visited during the summer. New lessons were learned from her data collected on volunteers who followed different sleep schedules. Her visit coincided with that of Yoshihiko Watanabe, a cardiologist from Tokyo Women's Medical University, Daini Hospital, Tokyo, Japan. After spending a 6-month sabbatical with us several years ago, Yoshihiko returns to Minnesota each summer to summarize data accumulated during the year. The results obtained during their short visit led to several abstracts listed in the bibliography below.

Manfred Herold, of the Universitätsklinik für Innere Medizin in Innsbruck, Austria, visited only briefly after participating in the Serono USA International Symposium on the Endocrinology of Aging (Tempe, Arizona, October 27-30), where he gave a presentation on "About-daily (circadian) and about-weekly (circaseptan) patterns of human salivary melatonin." The data he brought us from his laboratory shed new light on the 8-hourly (rather than circadian periodic) changes in endothelin-1.

Since November 1, we have had a new addition to our team: Naoto Burioka, Lecturer and Associate Professor in the Third Department of Internal Medicine, Faculty of Medicine, at Tottori University, Yonago, Japan. Naoto's interests are the chronobiology of asthma and the chaotic behavior of respiratory movement, the EEG and the ECG. He will be with us for 10 months on a foreign visiting scientist fellowship from the Japanese Ministry of Education and Science.

Locally, we have developed increasingly close relations with two professors. With Mark Engebretson, Professor of Physics and Director of the Center for Atmospheric and Space Sciences, Augsburg College, Minneapolis, we are learning about Pc pulsations and how these contribute to geomagnetic disturbances. With him, we hope to gain a better understanding of mechanisms underlying the effects of space weather on humans and other organisms. With Daniel Kaplan, Professor of Mathematics, Macalester College, St. Paul, we are learning about chaos analysis of chronobiological data. At the University, Dr. Keith Lurie with Dr. David Benditt are introducing the chronobiologic 7-day blood pressure monitoring project at the Rasmussen Heart Clinic.

In memoriam

In 1999, we sadly bade farewell to a noted colleague: Prof. Gunther Hildebrandt, emeritus head of the Division for Work Physiology and Rehabilitation Research of Philipps-Universität in Marburg, Germany, died on March 6, 1999, at 75. As a young scientist, Hildebrandt recognized the basic importance of biological rhythms. He participated from the outset in the building of chronobiology after World War II. In his theoretical contributions, he insisted on the systematization of variations in the normal range, formulating the spectrum of biological rhythms in different physiological functions. These rhythms play a central role in Hildebrandt's physiology of adaptations and in its applications, notably in the field of physiotherapy and spa medicine. Apart from chronomedical applications, another focus of his practically oriented interests was in the field of chronohygiene. Starting in the early 1960s, he worked on problems of night- and shift-work. There is nowadays a trend to make shift-work schedules more and more flexible, which is of growing importance. To contribute to biologically beneficial shift-work systems and in order to clarify individual differences in the tolerance of shift-work, Gunther Hildebrandt was concerned with the internal physiological temporal order and in how this is modified by unusual external schedules such as night-work. His most recent achievement was his book with Michael Moser and Michael Lehofer, "Chronobiologie und Chronomedizin: Biologische Rhythmen/ Medizinische Konsequenzen" (Hippokrates, Stuttgart, 1998). In addition to this comprehensive treatise, he is the author of another book on the biological week, perhaps his biggest contribution. He amassed a very great deal of evidence for the built-in nature of the week, tracing its origins to antiquity.

Chronobiology also lost two good friends in John Raidel (January 25, 1919-September 30, 1999), a *Gymnasium* classmate of Franz Halberg, and his wife Charlotte (June 29, 1921-August 13, 1999). John Raidel was an officer, pilot and instructor for the Hungarian Air Force during World War II.

In celebration

On a happier note, we mark the 62nd birthday of Masayuki Shinoda, president and chief executive officer of Colin Electronics, Komaki, Japan. Masayuki started a firm that has made its major worldwide concern the transition from **the** measurement of **the** blood pressure to the topic of this paper, the chronobiologic interpretation of blood pressure **series**. His generous gift of scores of monitors played a critical role in the development of a reference data base for blood pressure, from newborns to centenarians, in Asia and elsewhere. His portable, then ambulatory instruments were used in everyday life or in isolation from society for up to 267 days, or while lying in bed for days, or to assess effects from playing tennis. Pioneering studies in the field were

possible with hand-held tools, but it took automation to recognize and document disease risk syndromes, as outlined in two interpretive reviews this year (see bibliography below), setting the stage for preventive measures, for pre-habilitation. The ambulatory monitors are also useful in the context of rehabilitation, but may eventually obviate most of the need for treatment after a catastrophic illness, with early detection of an elevated risk in the otherwise asymptomatic patient. Masayuki Shinoda's monitors played a very great role in leading not only to the detection, but also to the treatment, of disease risk syndromes.

This year also saw the eightieth birthday (on October 29, 1999) of Theodor Hellbrügge, the leading pediatrician in the German-speaking world; the founder of social pediatrics; the author of the basic elements of social pediatric developmental rehabilitation; and above all the pioneer in the chronobiology of the human fetus, of the newborn, and of the developing child. To many, his social pediatrics is the cornerstone of mushrooming institutes after the model of his endeavor realized in bricks and mortar in Munich. To a few of us, his name is associated with his first scientific love affair, chronopediatrics, and, we hope, "on revient toujours a ses anciens amours." Theo Hellbrügge introduced behavioral science into pediatrics, and in so doing provided ethological measures for diagnosis and treatment, for what he conceives of as developmental rehabilitation. Literally as well as figuratively, Theo's most spectacular contribution is the Kinderzentrum in Munich, a model of an interdisciplinary institute for early diagnosis, early treatment and social integration of children with disabilities. Against the resistance of all authorities, he founded the first kindergarten in the world in which children with and without handicaps learn and interact jointly, in a continuation of the physiological pedagogy of the French physician Eduard Seguin and of the Italian educator Maria Montessori. More than 30 years ago, Theo Hellbrügge founded "Aktion Sonnenschein" ("the Sunshine Project") in Munich to benefit children with multiple disabilities.

Research

As reported earlier, endothelin-1 (ET-1), a very potent vasoconstrictor, undergoes an 8-hour rhythm in the absence of a detectable circadian variation in a study involving 7 clinically healthy subjects providing blood samples at hourly intervals for 24 hours. In another earlier study, circulating ET-1 was also found to be characterized by a 3.5-day component, which differed between clinically healthy subjects and patients at an elevated cardiovascular disease risk. Additional new data from the experimental laboratory provide further support to these earlier findings. Specifically, an about 8-hour component was detected for the population density of endotheliocytes in the capillaries of the connective tissue of the ear pinnae of mice. Moreover, an about half-weekly component was also prominent in the absence of a demonstrable circadian variation.

Leptin concentration determined in cord blood by Dr. Federico Perfetto and Dr. Roberto Tarquini of Florence, Italy, was found to be elevated in the presence of a family history of obesity on the paternal side, but not on the maternal side. This finding, published in Pediatrics, was selected for inclusion in the 2000 Yearbook of Obstetrics and Gynecology, to be published by Mosby, Inc. Cord blood leptin concentrations were also found to be higher in spring and summer than in fall and higher in infants born before vs. after noon. The results point to synchronizing environmental as well as genetic influences.

Research on blood pressure and heart rate variability (HRV) focused on effects from the environment (near and far), notably of helio- and geomagnetic disturbances. New results led to the formulation of a new branch of astrobiology, namely chronoastrobiology. The international project on the chronome mapping of heart rate variability continued. The long-term goals of the study are to investigate ecological influences on blood pressure, blood pressure variability and different endpoints of HRV, such as the standard deviation, the power in different spectral regions, the 1/f-like spectral behavior, the correlation dimension and complexity. The risk associated with a reduced 24-hour standard deviation of heart rate was confirmed and the relation to risk was found to be nonlinear. Some of the endpoints of HRV have been mapped as a function of gender, age and health status.

A patient with coronary artery disease was studied before and after coronary artery bypass grafting (CABG), collecting 7-day ECG records before and after CABG, from which different endpoints of heart rate variability were derived. Before CABG, but not thereafter, a 24-hour synchronized circadian rhythm characterized all variables examined. After CABG, the circadian amplitude of most variables was decreased. For some of the variables examined, the circadian component was no longer detectable with statistical significance at a trial period of 24 hours, notably in the case of the 5-min coefficient of variation in heart rate. Instead, an increase in the circaseptan amplitude of heart rate after CABG is statistically significant. Additional profiles obtained in the interim indicate that such a variance transposition was transient. A drastic decrease in heart

rate variability after CABG is in keeping with results reported by others.

The vascular disease risk associated with an elevated circadian amplitude of blood pressure was further confirmed in a study of over 2,000 subjects by C.H. Chen, using the left ventricular mass index as a surrogate outcome measure. As in earlier studies, the results show that "overswinging" carries a higher risk of morbid events than "non-dipping." Earlier studies by others first and then by ourselves indicated that while the mean value of blood pressure was linearly related to both the incidence of adverse vascular events and to the left ventricular mass index, the relation of risk with the circadian blood pressure amplitude was nonlinear. The nonlinearity of the relation between the circadian amplitude of blood pressure and risk (whether it is gauged by the actual number of morbid events or by the left ventricular mass index) was observed consistently in all subjects investigated. Too low a 24-hour standard deviation of heart rate has also been shown to be a predictor of risk, mostly for coronary artery disease and cerebral ischemic events. The relation between the 24-hour standard deviation of heart rate and the incidence of adverse vascular events that occurred within 6 years of the 48-hour profile obtained from each of the 297 patients was also shown to be nonlinear. For a wide range of standard deviations, there was no elevation in cardiovascular disease risk, but once a threshold value was exceeded, the risk increased drastically and with statistical significance.

Both heart rate and the standard deviation of heart rate have been shown to change with an about 10.5-year cycle similar to that of Wolf's number, used as a gauge of solar activity. The biological decade has become a component of the spectral element of chronomes and an important piece of control information. Just as the stages of the biological year, month, week and day can be confounders when they are not assessed, the solar cycle stage should also be recorded. Such a periodicity in human heart rate has been documented on the basis of two unique data series. One stems from 31 years of self-measurements carried out 5 to 6 times a day on most days by Dr. Robert Sothern. The other series consists of around-the-clock data at 15- to 30-minute intervals for 11 years obtained with an ambulatory monitor by Dr. Yoshihiko Watanabe. An about 10.5-year variation has also been documented for mortality from myocardial infarction recorded in Minnesota from 1968 to 1996; it accounts for an excess mortality of 220 cases per year (an about 5% increase) at times of maximal solar activity in comparison with times of minimal solar activity.

The task ahead is to define the source and the mechanism of the risk of adverse vascular events, including, beyond myocardial infarctions and strokes, relations among physiological variables assessed longitudinally. Among mechanisms of heart rate variability, the autonomic nervous system comes to mind. Not only have signs of reduced vagal activity been associated with an enhanced risk of sudden cardiac death, but impaired heart rate variability has also been shown to serve as a predictor of mortality in patients with a variety of other vascular diseases.

Reduced heart rate variability on days of high magnetic activity vs. quiet days has now been documented in the longitudinal ECG record of Dr. Kuniaki Otsuka, a clinically healthy man. The decrease in heart rate variability is validated statistically in both the time and the frequency domains, on the basis of the coefficient of variation of R-R intervals (analyzed in consecutive 14.4-min intervals over a 7-day span) and of the total spectral power, respectively. Moreover, the decrease in spectral power was found to be primarily contributed by a decrease in power in the "very low frequency" range (with periods in the range of 6.5 to 333 sec). The decrease in heart rate variability is much less pronounced in two other spectral regions centered around 10.5 sec ("low frequency") and around 3.6 sec ("high frequency"). If confirmed on additional cases, this result may point to some underlying physiological mechanism responsible for the physiological response to changes in magnetic activity other than the parasympathetic, usually identified with spectral power in the 3.6 sec region.

On December 24, Othild and Franz returned from Antarctica, where they monitored heart rate and blood pressure on themselves, to look for a combination of jet and equatorial lag, or possible transmeridian and trans-parallel lag. Their data show the anticipated jet lag, the rules of which we documented decades ago. For picking up any effects of latitudinal crossing, the study of many more cases and additional variables, notably of salivary melatonin and cortisol, will be needed to look at the ramifications of impressions gained from this and earlier monitoring and other investigations. A latitudinal effect reported by us earlier for the chronome of melatonin was most recently complemented by Lennart Wetterberg's finding of a weak latitudinal effect upon nightly melatonin. It seems possible that the extension from night to day of the latitudinal study would be informative, as is a meta-analysis of data published by others concerning a lack of an age effect upon nocturnal melatonin. When data taken off published graphs are log-transformed, the age effect upon amplitude stands out clearly, a reminder that

in dealing with cycles, there is no reason to discard data because they are too low at certain times; the main information may be at those particular times. There is a precedent of liver glycogen rhythmicity, which persists after starvation, as shown originally in the Biochemical Journal by Ågren, Wilander and Jorpes [1], and then quantified by Erhard Haus [2].

During the past year, the circumstance that on an unacceptable schedule the periods found are very close to 24 hours, which we had reported with Hugh Simpson in Arctic Anthropology [3], was confirmed; but today, a broader chronome view is indicated in the light of the following bibliography.

As a follow-up of the visit of Dr. Yuji Kumagai (Lecturer, Department of Clinical Pharmacology, Kitasato University East Hospital, Sagamihara, Kanagawa, Japan) and Ken Yasaka (General Manager, R&D Division, A&D, Tokyo, Japan), the A&D company has offered us a very great reduction in price of instrumentation for conducting the research on stroke prevention worldwide. Several collaborators have already availed themselves of this very generous offer. In addition to the city of Roseville, these include groups led by Dr. David Benditt, Dr. Keith Lurie and the Rasmussen Heart Clinic at the University of Minnesota; Dr. Katarina Borer at the University of Michigan in Ann Arbor; Dr. Federico Perfetto and Dr. Roberto Tarquini of the University of Florence, Italy; Dr. Salvador Sánchez de la Peña in Mexico City, Mexico; Dr. Jarmila Siegelova in Brno, Czech Republic; and Dr. Ziyan Zhao in Jinan, People's Republic of China. The data thus collected will be flowing in for chronobiologic analysis.

We thank the many friends and co-investigators who have made our lives rich and exciting. To all, we wish the best of health and productivity in the new millennium, and the completion of the numerous endeavors many of us have jointly begun.

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