

## 1997

The appended bibliography shows some names among the many who gave us a chance in 1997 to learn from them and to help in placing their results into print. Indeed, we have become exclusively a design and analysis laboratory since our chemistry and histology laboratories, built for us by NIH, NSF and NASA, were expropriated. This occurred before I passed 70 years of age, well over 8 (perhaps 10) years ago, while NIH continued my career award. We are trying to make a virtue of each of our local shortcomings. The first title of this year's bibliography shows that a former physician fellow in our laboratory, Salvador Sanchez de la Pena (of pineal-pituitary-adrenal feedside fame), who did his second doctorate with Hugo Arechiga and us, is active and occupies more and more important research positions in his native Mexico City's and his country's health care system. Indeed, Salvador has persuaded Mexican nurses to do a combination of self- and colleague measurements of blood pressure and heart rate. This most successful endeavor sets an example for many to follow. The nurses take hourly measurements themselves during waking; during sleep they have the cuff on and their nursing colleagues take their pressure. They are now about to implement 7- day series rather than 2-day profiles, so as to obtain their individualized reference values for future sphygmochrons, computer- prepared profiles to be interpreted in the light of our 7-day reference data base, serving a double purpose in keeping with the project on the BIOSphere and the COSmos, briefly BIOCOS. The project aims at concomitant physiological and physical monitoring for health care and more basic purposes, the scrutiny of effects of physical factors from near and far.

Mexico is in the forefront of chronobiology. It is home to many young, interested students, and it was great fun to address them in a course on clocks to which Salvador and I added time structures, i.e., chronomes. The chronobiologists Hugo Arechiga, the president emeritus of the Mexican Academy of Sciences, and Maurizio Garcia Sainz, as secretary of the Academy of Medical Sciences and perhaps its next president, occupy the leadership positions that could bring chronobiology into health care by appropriate guidelines for clinical use, endeavors that are ongoing in Russia, where on June 30 the Russian Academy of Medical Sciences had a special meeting on BIOCOS, and where Acad. Asarii G. Gamburtsev will further propose interdisciplinary activities nationwide along similar lines in December 1997.

Japan is a chronobiologically very advanced country. Even if it lost its administrative leader, the late Kentaro Takagi (former president of Nagoya State University and a member of the Diet), Teruo Omae, in a leadership position at the National Center for Cardiovascular Diseases in Osaka, is still active. The next two titles in the bibliography below take us to Kuniaki Otsuka and his team, to which we are glad to belong. Kuniaki's most recent contribution, following upon many others, has shown how rhythms organize chaos. A number of titles document his success in so doing. When I had an opportunity to visit him in Tokyo a while ago, he told me that he had a very pleasant surprise for me. It was the data base for a new risk syndrome. He had found in a prospective 6-year study that catastrophic events were much more frequent in patients with a large circadian amplitude of blood pressure. His finding culminated in statistically highly significant outcomes that underlie the condition of Circadian HyperAmplitudeTension (CHAT).

Kuniaki thus took to the clinic what Julia Halberg with her mother had documented in many around-the-clock studies decades ago on rats, in groups of 40, each group studied around the clock at 4-hour intervals for 24 hours, repeatedly for the rats' lifetimes. There was on occasion, fleetingly, a very large increase in the rats' circadian blood pressure amplitude, preceding the increase in rhythm-adjusted mean, in the Midline-Estimating Statistic Of Rhythm (MESOR). The amplitudes were unbelievably large. As a concerned father I was not sure that those very large changes should be published, until the late Fred Bartter encouraged Julia and me to do so (Halberg J. et al., *Int. J. Chronobiol.* 7: 17-64, 1980).

The data of Yuji Kumagai followed, extending the scope of the rodent studies to humans, showing that the echocardiographically determined, somewhat enlarged left ventricular mass index (LVMI) was associated with an enlarged circadian blood pressure amplitude, in the absence of an increase in MESOR (Kumagai et al., *Chronobiologia* 19: 43-58, 1992). The crowning was the result by Kuniaki Otsuka, which led to the new risk syndrome, CHAT.

We could have called the not-so-new category of conditions that allow the chronobiologic detection of a very high risk of developing a disease by a new term, yet it seemed reasonable to use the term "syndrome" (literally "running" [dromos] + "together" [syn]) and to apply it to the condition of a chronome alteration that runs together with a high risk of catastrophic vascular, oncological or other disease. Rather than coining a new term for CHAT and other conditions that need chronobiologic methods for their resolution, and that characterize apparent health, the old term, "syndrome", offered itself, and rings a bell. Whether or not a constellation of signs and symptoms may eventually be identified for each risk syndrome, at the outset blood pressure overswinging (CHAT, Circadian HyperAmplitudeTension), which carries a high risk of ischemic cerebral and other vascular disease, is defined merely by overswinging and the elevation of the risks of adverse events. The possibility cannot be ruled out that the disease has already set in in people with CHAT, but thus far we have no indication that this is the case. At this time, we can define the risk syndrome with the foregoing qualification. CAHRV is another vascular risk syndrome. We know from Kuniaki Otsuka that it is a Chronome Alteration of Heart Rate Variability. Thanks to Kuniaki, data became available to combine chronos and chaos into the chronome, as given in detail in reference 2294, with background in 2296.

Dr. Otsuka is now the initiator and principal investigator of an international study involving 7-day or longer ECG monitoring. I am very happy to have been a subject before and after a quadruple bypass operation on October 29, 1997 (my second such surgery, following a triple bypass at Stanford in 1981). Incidentally, a dissociation of heart rate from blood pressure was found on myself after the bypass operation, with the heart rate circadian of extremely low amplitude, while the blood pressure adopted a circasemidian frequency due perhaps to twice-daily Betapace treatment.

But enough of myself. We must congratulate Vaclav Havel, president of the Czech Republic, for just having named Jarmila Siegelova as a full professor. A very fruitful cooperation continued with Jarmilka in 1997 as in preceding years. Othild Schwartzkopff, my pediatrician companion, and I had a chance to see her and her hospital in Brno, and we enjoyed the visit of Pavel Homolka, her clinic chief, to Minnesota in the summer of this year, for a span of several months shared with the

Mayo Clinic. We are eagerly awaiting Pavel's data to complement those of the Yuzo Saito, Nelson Marques and Halberg families, to look at the broader-than-circadian chronome adjustment after transmeridian and transequatorial flights, respectively. Jet lag involves more than circadians: the circadian-circaseptan intermodulations open a new chapter with applied consequences in aviation and shift-work concerns.

Julio Ardura in Valladolid, Spain, with Miguel Revilla, contributed to the question of the chronos vs. chaos nursery. He showed that inadvertently we may have a chronos nursery. But is it the right chronos ?

Dr. Zhengrong Wang, a former fellow of this laboratory, returned to Minnesota from Chengdu, China, where he is professor and head of biophysics and vice-dean of the school of basic medicine at the West China University of Medical Sciences. Zhengrong demonstrated rhythms in 1) myosin heavy chain contractile protein gene expression, in 2) contractility and in 3) left ventricular pressure, with increasing circadian amplitudes from 1 to 3, showing the genetic, other intracardiac and extracardiac contributions to the rhythm in blood pressure. In the context of Kuniaki's study, Zhengrong also recorded his own ECG for over a week in Minnesota, and we trust he continues his monitoring in Chengdu.

A new student by correspondence was Mary Jane Thaela, originally from South Africa, who did her thesis in Lund, Sweden. Mary Jane deserves the credit for contributing data compatible with the demonstration of a prominent multiseptan aspect in the pancreatic digestive function of piglets. Thus, she extended to still another species, the piglet, the scope of the prominence of the biological week, so far demonstrated in hundreds of human newborns in Minnesota, the Czech Republic, Spain, Japan, and first and foremost in Italy and Russia. A hint of transient circaseptans was also found in the data of Antoni Diez-Noguera of Barcelona, Spain, on young rats, and in certain unicells. Most recently, in data that as yet are unpublished on crayfish activity early in life, Maria Luisa Fanjul Moles of the Autonomous University of Mexico City added weighty evidence that again extracircadians, notably multiseptans (multiples or submultiples of the biological week), are larger in amplitude than circadians early in crayfish development. Actually, the crayfish, early in life, is characterized by prominent about 5- day components. These findings complement those made in the data of Leland Edmunds on mitosis of *Euglena gracilis* Klebs, which after mutation changes from circaseptan to circasemiseptan, in keeping with earlier findings on *Acetabularia* after enucleation. The fact that circaseptans can change into circasemiseptans following enucleation or mutation should be viewed in the context of the effect of a circadian mutation in the hamster which is compatible with a change from a circaseptan to a circasemiseptan pattern. The data on which such conclusions are based are limited. This criticism is just, and more data are needed. The remark that circaseptans are purely societal is unwarranted; it can originate only from scholars outside medicine. This proposition could have been rejected already by Hippocrates, Galen and Avicenna, who observed that the period between the onset of a disease and its resolution as a crisis or lysis (as death or survival) occurred as a rule 7 days after the onset, whether that onset (or a transplant in our time) occurred (or was carried out) on one or the other day of the week (the single stimulus carries no 7-day information).

Locally, Mary Jo Rawson, a student we share with James Holte in engineering, has documented still another case when the human heart rate dissociates from blood pressure, showing a statistically

significant phase-drifting circaseptan of heart rate during a stretch when, to start with, there is no circaseptan demonstrable in systolic, diastolic or mean arterial blood pressure, whereas when (after a while) the circaseptan becomes prominent in blood pressure, it is strictly 7-day synchronized, during the span of the phase- drifting heart rate. Mary Jo was also first to record an unpredicted (and hence in need of confirmation) statistically significant increase in circaseptan blood pressure amplitude during emotional depression. The circasemiseptans have been scrutinized by Mikhail Denisov of St. Petersburg, Russia, who may be in a position to check on Mary Jo's finding, as could Nadejda Madjirova in Plovdiv, Bulgaria, and, we trust, others.

The cooperation with Rina Zaslavskaya continued. Her newest finding, presented at the meeting of the American Society for Hypertension in San Francisco in May, reported exceptional data, much needed and to be amplified in Kuniaki's 7-day ECGs. She had mapped circaseptans in a number of cardiovascular variables from cardiac output to peripheral resistance every 4 hours for 7 days. More power to her. We enjoyed having her as a house guest in Minnesota (even if we apologize for having spent too many nights working on her data in the laboratory) and in Francine's home in Tiburon on San Francisco Bay, where Rina, Germaine, Othild and I appeared for a most enjoyable visit during the meeting. Thanks are due to Francine and her husband Terry for too many things to enumerate, including Terry's paper on the dentist's role in chronobiology, to appear early next year.

Brunetto Tarquini, with his colleagues Roberto Tarquini and Federico Perfetto, discovered the peculiarities of the chronome of endothelin-1 (ET-1). He found extracircadian prominence in this most important vasoconstrictor: first and foremost, a 3.5-day periodicity rather than a circadian rhythm, and also an about 8-hourly component, which was independently also found in ET-1 data of Manfred Herold from Innsbruck, Austria. Manfred's data are particularly important since in the same students in whose endothelin-1 a circaoctohoran component predominates, cortisol had its usual circadian rhythm as the most prominent aspect, without a statistically significant 8-hour component.

Most challenging is Brunetto's and his colleagues' finding that at different times of day, melatonin undergoes different changes along the 1-year scale. When he mapped circulating melatonin every 4 hours for 24 hours in 171 patients, the daytime data underwent a circannual rhythm. By contrast, the nighttime data showed a half- yearly pattern which is compatible with the half-yearly change in geomagnetics, emphasized by Armin Grafe of Niemegek, near Berlin. This finding at middle latitudes can be compared with one at 65.00 degrees N in Oulu, Finland, where the noon melatonin values (the only ones available for metachronanalysis) showed an about-half- yearly pattern. Walter Randall in Iowa had noted that sunshine may be weaker and geomagnetics much stronger near the pole. The melatonin analyses along the 1-year scale fit his description and extend his suggestion to the pineal, a putative receptor of feedsideward effects of the cosmos upon us, with geomagnetics perhaps modulating or overcoming the effect of sunshine at middle latitudes and near the pole, respectively.

Indeed, in the budding field of chronoastrobiology, a number of our earlier findings were complemented by new results from the Institute of Pediatrics of the Russian Academy of Medical Sciences, headed by two leaders in chronopediatrics, Academician Mitrofan Studenikin, who had shown that children's heart rate is higher during daytime than during nighttime sleep, and Dr.

Galina Yatsyk, who had focused on the adrenocortical cycle of the newborn already during her thesis. The head of the chronobiology team is Elena Vasilievna Syutkina, with Alexander Grigoriev, Maria Mitish, Tatiana Turti and first and foremost Anatoly Masalov. She showed that the circaseptan period of the heart rate and blood pressure of human babies monitored for several weeks correlated with the period of the contemporaneous about-weekly component in local geomagnetic disturbance, the K index. This achievement must be aligned with earlier demonstrations of the group of Elena Vasilievna in documenting effects of betamimetics lasting into adolescence, documenting the effect of an altered periodicity of blood volume and blood oxygenation upon subsequent neurological damage, in showing solar cycle-related about 11-year changes in babies' blood pressure, among very many other findings.

There is a German verse: "Die Geister die ich rief, die werde ich nimmer los" (I cannot dispose of the spirits I called [in coining and emphasizing the importance of circadians]). This applies to the many most meritorious current scholars working on circadian systems; the clock investigators certainly dominated a meeting and course in chronobiology in Mexico, and even a major prior contributor to circaseptans converted to clocks. It would be difficult, however, to think further of neural master clocks such as the suprachiasmatic nuclei (SCN) when the "time-keeping PER protein" is found in so many extracerebral sites (Pennisi E. Multiple clocks keep time in fruit fly tissues. *Science* 278: 1560-1561, 1997). The concept of a circadian system with a neural master clock was incompatible with the demonstration in our laboratory of the persistence of the circulating blood eosinophil rhythm after stepwise ablation of the brain (*Endocrinology* 76: 895-901, 1965), including a suprapontine brain ablation, documented in the 1960s. It is incompatible with the demonstration that the removal of the suprachiasmatic nuclei, the presumed =B3master clock=B2, is compatible with the persistence of a large number of circadian rhythms, such as that in telemetered core temperature, which to the naked eye appears to be very much disturbed, but for which by a time-microscopic method the persistence of a rhythm can be documented with statistical significance. Persistence after the histologically validated bilateral SCN ablation is further shown by Larry Scheving for basic cellular rhythms such as those in mitosis of cornea and in different parts of the digestive tract, including circadian rhythms in DNA labelling in the digestive tract. The loss of a rhythm in corticosterone was reported with 6-hourly sampling, but with 4- hourly sampling, very large within-day changes ( $P < 0.001$ ) can be demonstrated in circulating corticosterone. The SCN unquestionably is an important mechanism of phase and amplitude adjustment, but the reduction of the amplitude to 0, namely a complete loss of rhythm, has been documented thus far for only a few variables such as motor activity or water consumption, but not in alcohol consumption nor in the variables mentioned above.

We could rename the cell a clock, but the heuristic value of such an endeavor is to be questioned. We cannot say "first things first" and focus on circadians if the cancer patient receiving an immunomodulator just by circadian scheduling may see the growth of a malignancy enhanced rather than inhibited by the circadian-adjusted treatment, simply because circaseptans are disregarded (Ulmer et al., *In vivo* 9: 363-374, 1995).

The chronome clearly involves multifrequency rhythms, not just the circadian system, many rhythms intermodulating by feedsideways. But these rhythms are just one element and the endpoints from probabilistic chaos just another element, thanks to Kuniaki Otsuka's contributions. Both elements undergo the third element of trends. All these elements, while anchored in our

genes, still resonate with the chronomes of the cosmos, in response to which they entered the genome in the first place. We must map internal (with external) chronomes from womb to tomb so as to sample them strategically, to bring about a health care of prevention where we focus our means upon those who are at risk rather than treating the population as a whole. This focus on prevention starts at birth, or actually in utero. The abstract of the manuscript on blood pressure monitoring says it all: chronobiologic monitoring FOR WEEKS at the proper ages in those at risk may save much post-catastrophic care FOR YEARS.

It was a pleasure to be with Miroslav Mikulecky in the High Tatras and in Nove Zamky to discuss the roots of chronobiology in the cosmos. As discussed in a paper invited by the Mendelianum, available on request by e-mail only, Gregor Mendel was a chronobiologist, and his legacy is more than the genetic aspects of our time structure. The genes have to, and did, get the information from the environment. We can show resonance with a number of distant drummers objectively, and will learn more and more about the solar wind and the interplanetary magnetic field and about magnetic storms that, as Juan Roederer put it, can be hazardous to our health. As Juan also put it, "... the implications of solar variability-induced effects on biota and human health, however small, could be far-reaching. Leaving aside the potential impact on preventive medicine, health care and insurance, it would be of basic importance to chronobiology" (Roederer J.G. Are magnetic storms hazardous to your health? *Eos, Transactions, American Geophysical Union* 76: 441, 444-445, 1995). "Rather than relying solely on a master clock in the brain to coordinate all body rhythms, for these many other clocks", Steve Kay of the Scripps Research Institute proposes, "the true master switch is just sunlight" (Pennisi E. Multiple clocks keep time in fruit fly tissues. *Science* 278: 1560-1561, 1997). The effect of light is indeed pervasive. We knew in the 1950s that our then-discovered rhythms in RNA and DNA formation, as well as those in mitosis in circulating corticosterone and glucose, among others, could all be switched by manipulating the lighting regimen (Halberg F., Barnum C.P., Silber R.H., Bittner J.J.: 24-hour rhythms at several levels of integration in mice on different lighting regimens. *Proc. Soc. exp. Biol. (N.Y.)* 97, 897-900, 1958). But not ONLY sunlight in 1997, as we look at Brunetto Tarquini's documentation of the role of geomagnetics complementing light, perhaps more and more so as we near the pole.

It was a pleasure to see our chronobiology on the cover of Nadejda Madjirova's book, with 1. the major features of the cosmos and its effects upon us, 2. the persistence of rhythms with reduced amplitude and advanced phase after SCN ablation, and with feedsidedwards all on its cover.

As always, we had an incessant stream of visitors whom we greatly value. Yoshihiko Watanabe, who came from Tokyo, has now completed ten years of dense around-the-clock blood pressure and heart rate monitoring and has documented the non-drug and drug therapy of CHAT. Andi Weydahl, from Alta, Norway, within the Arctic Circle, does the chronobiology of exercise, cooperating with Bob Sothorn (who is continuing his invaluable 30+-year series of self-measurement). Yuji Kumagai, who also returned from Japan, further follows the tradition of self-study, as well as documenting the effect of carnitine on heart rate variability and motor activity, showing a phase delay for heart rate, reported by us with him earlier in health, among other findings. As noted, we were pleased to have with us Rina Zaslavskaya, who is responsible for the chronotherapy of high blood pressure documented by a handicapped design. A book on chronocardiology in English is a joint aim.

Through Pat Delmore and contact with Tom Bennett of Earl Bakken's Medtronic, we could report around the world, in Russia and in the Czech and Slovak Republics, on Medtronic's new implantable device providing beat-to-beat right ventricular systolic and diastolic blood pressure and heart rate for spans of 15 months or longer, from an ambulatory patient. The analysis revealed a circadian-to-circasemiseptan variance transposition. The meaning of such challenging changes, associated in this case with steroid treatment, remains to be clarified. We learned this year again from Earl's scrutiny of the literature. He contributed not only the pacemaker, but also free-running as an analogy.

We were very pleased to confirm the hard data on CHAT in terms of actual outcomes with an invaluable data base by Chen-Huan Chen of Taiwan, whose proxy outcome of a left ventricular mass index (LVMI) was available for each of 424 patients. The net result was that the proxy outcome LVMI corroborated the result of the actual adverse event by revealing what may be most interesting to industry, namely a threshold value for the circadian blood pressure amplitude, up to which there is no change and after which there is a marked increase both in LVMI and in adverse events.

Jong Lee and her niece Mary Lee, still in high school, completed meritorious studies both on blood pressure self-monitoring with a look at the cold pressor test along the scales of a day and a week and on an erythropoietin receptor and the antibody to it, the former from a circasemiseptan as well as a circadian, the latter as yet only from a circadian viewpoint.

In the local dental school, Frank Raab's classical results on fleeting CHAT, including his demonstration that the same surgery raises blood pressure in the morning and lowers it in the afternoon, was accepted for publication in the Journal of the American Dental Association. It was a pleasure to see Professor of Oral Medicine Nelson Rhodus present the results of the group in the local dental school in St. Petersburg, Russia. Relations with Prof. Rhodus, Dr. Raab and in particular emeritus professor and dean Erwin Schaffer may well be strengthened next year, when we expect the return of Prof. George Katinas, who was sent to our laboratory by the then- USSR over 20 years ago and now is invited for a Lasby Professorship in the School of Dentistry. A separate report by Othild Schwartzkopff, with whom I have the privilege of sharing my life, is self-explanatory, and notes some of those events I had no opportunity as yet to mention. I must repeat in any event the splendid hospitality of Mikhail, Clara and Arcady Blank in St. Petersburg and of Elena Vasilievna Syutkina in Moscow, and that of many others.

Most important, perhaps, of all endeavors by our many friends was the ability of Dr. Syutkina to convene a meeting of the Russian Academy of Medical Sciences, specifically to discuss now her as well as our project on "The BIOSphere and the COSmos" (BIOCOS), advocating concomitant physiological and physical monitoring for basic purposes to detect the effects of the cosmos, but also for applied indispensable reference values for blood pressure and heart rate, among other variables studied opportunistically. My very hearty thanks for this achievement in administration, which equals Elena's major earlier original scientific contributions.

If the average number of full publications is about 1.5 per active scientist, the larger number of full papers in the following bibliography is due to the many colleagues, mostly friends with whom we have the privilege of cooperating and, on the Minnesota side, to the untiring activity of Germaine

Cornelissen. Germaine is able to initiate, plan, design and analyze job after job. The laboratory's agenda could not be in better hands. My role is reduced to having immortalized her again in St. Petersburg, as she was earlier in Ekaterinburg, by the use of her name for the Cornelissen-series to describe circaseptan-to-circadian and related amplitude ratios of rhythms (at the XXXIII International Congress of the International Union of Physiological Sciences in St. Petersburg, July 1-7, 1997).

May every day of yours be a healthy holiday; and if your name appears neither in this letter nor in the bibliography, I apologize. I owe so many so much; I try to do justice, at least to a few.

Gratefully, Franz

PS: When I was asked by Salvador to be a founder of a new journal and to write a note, I included the following table in the manuscript. Quo usque tandem:

Who will guard the guardians?

To err is human; to forgive is divine; but to persist in error is diabolic

Question: WHICH OF THE FOLLOWING ANACHRONISMS IS POTENTIALLY HARMFUL?

1. "Automobiles travelling on country roads at night must send up a rocket every mile, then wait ten minutes for the road to clear" (i)
2. "If a driver sees a team of horses, he is to pull to one side of the road and cover his machine with a blanket or dust cover that has been painted to blend into the scenery" (i)
3. "In the event that a horse refuses to pass a car on the road, the owner must take his car apart and conceal the parts in the bushes" (i)
4. "If the initial screening blood pressure values (in mm Hg) are <130 systolic and <85 diastolic, recheck in two years" (ii)
  - i. "Rules of the Road" drafted c. 1900 by (Pennsylvania) Farmer's Anti-Automobile Society (READ: JNC V; see ii below). Provided by Anne Mackereth, Minnesota Department of Transportation Library, Mail Stop 155, 395 John Ireland Blvd., St. Paul, MN 55155.
  - ii. Recommendation of the Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch. Intern. Med. 153: 154-183, 1993. NIH Publ.

No. 93-1088, March 1994. Reprinted by Citizens for Public Action on Blood Pressure and Cholesterol.

Answer: THE FIRST THREE "RULES OF THE ROAD" ARE OBVIOUSLY RIDICULOUS AND HENCE HARMLESS; IN THE CASE OF RECOMMENDATION 4 ABOVE, A 720% INCREASE IN THE RISK OF STROKE MAY REMAIN UNRECOGNIZED (1-3).

Someday, governmental apologies will be in order, along the lines of President Clinton's formal apologies to subjects of radiation experiments conducted during the Cold War and to black subjects of the Tuskegee Syphilis Study, who were not told of the nature of their illness and were left untreated for decades after penicillin was recognized as a cure for syphilis, or the U.S. government's apology to American citizens of Japanese descent interned in World War II. As to the wrongs of today for which future presidents may apologize, we need not stand silently by while time-unqualified casual spotchecks on roller coasters, e.g., in the case of measuring THE blood pressure or THE pulse, interpreted in the light of fixed limits, remain the state of the art of today's not-so-preventive health care.

1. Halberg F., Cornelissen G., International Womb-to-Tomb Chronome Initiative Group: 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: Fairy tale or reality=A0? Medtronic Chronobiology Seminar #8, April 1995, 12 pp. text, 18 figures. Accessible in part on the Internet site of the Chronobiology Laboratories, <http://revilla.mac.cie.uva.es/chrono>
2. Otsuka K., Cornelissen G., Halberg F. Predictive value of blood pressure dipping and swinging with regard to vascular disease risk. *Clinical Drug Investigation* 11: 20-31, 1996.
3. Otsuka K., Cornelissen G., Halberg F., Oehlert G. Excessive circadian amplitude of blood pressure increases risk of ischemic stroke and nephropathy. *J. Medical Engineering & Technology* 21: 23-30, 1997.