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With the season's greetings, we report several unpublished or published findings, even if we regret that we are not sending reprints:

1. For an alga, *Euglena*, a eukaryotic unicell, in data which Leland Edmunds (now of the State University of New York at Stony Brook) had sent to us in the 60s, Germaine's reanalysis reveals a 7-day pattern of cell division in the wild type which becomes half-weekly (circasemiseptan) in a mutant. This finding is reminiscent of the *Acetabularia* pattern before and after removal of the nucleus (1) and of the anucleate thrombocyte's half-weekly pattern (2). On revient toujours a ses anciens amours.

2. Reanalyses of the centenarian data from Bulgaria (3) and of new data on old people from Tyumen (Siberia), Russia, analyzed by Denis Gubin of Tyumen, who is now studying with us, reveal a very prominent biological half-week and week of both human blood pressure and heart rate. The week and half-week have a way of appearing when we are as yet helpless or again more or less weakened, as is the mutant of Euglena, apparently less adaptable because of its defects in chlorophyll machinery.

3. Jarmila Siegelova, Bohumil Fiser and Jiri Dusek of the Department of Pathophysiology at Masaryk University, Brno, Czech Republic, visited us in January and analyzed a number of data sets, showing with the endogeneity of the weekly component of blood pressure and heart rate (when summarized in relation to the moment of birth) also an exogenous effect for the case of diastolic blood pressure. Although the exogenous component is much smaller than the endogenous one, and even if the underlying factors are not known, its mere presence suggests for those interested in optimizing the physical environment of the NICU that this may be possible by imposing appropriately scheduled environmental cycles in the isolette.

4. Jack Falcon of the University of Poitiers, France, extended the persistence of the biological week in vitro to more than two cycles and made the observation that the pineal may respond to light and darkness in a superfusion setup, since the circadian which was much less prominent than the week in pineals superfused in continuous darkness was very large in alternating light and darkness, even if the circaseptan modulation is clearly apparent.

5. Data from Yoshihiko Watanabe (Tokyo Women's Medical College, Daini Hospital, Tokyo), as analyzed by him while he spent much of this year with us, allowed the documentation of what Yuji Kumagai's study with echography had implied (4), namely that Circadian HyperAmplitudeTension (CHAT) is most frequent when the MESOR of blood pressure is between 130 and 140 mm Hg, in transition between normotension and hypertension. He demonstrated the importance of 7-day monitoring, so that people who should be treated for circadian hyperamplitudetension are treated rather than left untreated, their high risk of stroke notwithstanding, or if they are properly diagnosed that they receive timed treatment rather than long-acting drugs that may jeopardize their health when a pressure which is already too low for part of the day is lowered further by long-acting drugs. The increase in vascular risk associated with CHAT had been demonstrated earlier in a 6-year prospective study by Kuniaki Otsuka (5, 6).

6. All of these findings underline the resolution in Brussels in March 1995 to introduce chronobiology into the mainstream starting with the 7-day monitoring of blood pressure (7). This resolution and the Introduction to Chronobiology (8), kindly preprinted or printed by Earl Bakken, are available free of charge while supplies last from Patrick Delmore (Director of

Communications, Medtronic Inc., 7000 Central Ave. N.E, Minneapolis, MN 55432, USA; 612-574-3725 phone; 612-574-4563 fax).

7. Yoshihiko Watanabe also demonstrated that self-hypnosis (autogenic training) can help lower the excessive circadian amplitude, and further that when autogenic training fails, certain beta-blockers serve the same purpose. Many more findings are apparent from the titles of our publications, some of them part of an entire issue of *In vivo*, with more publications dedicated to Erna's memory beyond those listed below.

8. This summer, (Professor of computer science) Miguel Revilla Sr. and Carmela Rodriguez (a physician interested in smoking cessation), husband and wife, and their teenage sons Miguel Jr. and Emilio, of the University of Valladolid, Spain, visited our laboratory. A set of programs, the Chronomova, is about to be ready for those interested and will be available on the Internet.

9. Ramon Hermida (Professor and Director, Chronobiology Laboratories, University of Vigo, Spain), the author of a most useful set of programs on the Macintosh, lectured at the Supercomputer Institute, as did Bohumil Fiser of Masaryk University (Brno, Czech Republic) and Donald Marquardt of Athens, Delaware, former head statistician at DuPont, past president of the American Statistical Association, pioneer of nonlinear rhythmometry and mentor of chronobiometry, who had made the use of spectra on unequidistant data into a reality. Don Marquardt feels that the time to bring chronobiology into the mainstream of medicine is now, and CHAT is the way to do it. Others visited from around the world, notably Dr. Alvaro Ronco from Uruguay, with whom Germaine and Miguel analyzed cancer registry data.

10. Waldemar Ulmer's (Institute of Biochemistry, University of Goettingen, Germany) use of the Schroedinger equation to compute resonant frequencies of ions diffusing in a weak magnetic field may have provided a physicochemical basis for what Juan Roederer, whom we greeted for a lecture earlier this year, called the atavistic week in a lead article in *Eos*, publishing the confirmation of distant drummer effects for 30,000 geophysicists. Cooperation with physicists has been invaluable in the past. We can only hope through Tamara Breus and Kirill Pimenov of the Space Research Institute in Moscow that there may be much further progress in the budding field of chrononeonatology, in cooperation with the group of Elena Vasilievna Syutkina of the Institute of Pediatrics of the Academy of Medical Sciences, also of Moscow.

11. With Julio Ardura and Jesus Andres (also of the University of Valladolid, Spain), Miguel Revilla documented that in intensive care units, there may be quite a few unintentional periodicities, and

as the chronome of the human infant is being described, we may learn how to optimize the environment accordingly.

12. Yoshihiko's son Fumihiko provided around-the-clock data for 40 days on a healthy full-term newborn, continuing measurements at intervals thereafter. The week and half-week are prominent during the first two weeks of life, but in Fumihiko they promptly decrease in amplitude thereafter, at variance with the behavior in prematures of the circaseptan and circasemiseptan components.

13. At year's end, Leopoldo Garcia Alonso came from La Coruna, Spain, with a complement to the data on Fumihiko Watanabe by some 40 healthy Spanish babies to show that as a group basis, there is a decrease in both circadian and circaseptan amplitude from the first to the second week of life. We have newly found a circaseptan modulation of the circadian amplitude of systolic and diastolic blood pressure in addition to the circaseptan-circadian superposition.

14. At Thanksgiving, Roseville mayor Dan Wall monitored himself for 7 days including the time of his duties as timekeeper at the championship game of a local ice hockey tournament in which his son played. The excitement sufficed to render his amplitude larger than acceptable. Earlier and thereafter, however, the amplitude was acceptable; overall, because of the 7-day monitoring span, his health could be ascertained, and he served as yet another example of the importance of refraining from diagnosing CHAT with no more than a 24-hour profile. With proper documentation, however, the diagnosis of CHAT can become the basis of a campaign for stroke prevention.

15. The prevention of stroke and other diseases of adults and in particular of those of the "second childhood" starts during pregnancy. Cristina Maggioni (Assistant Professor of Obstetrics and Gynecology, University of Milan) organized a truly broad and all-encompassing meeting in chrono-obstetrics. There were many outstanding contributions using hyperbaric indices and other parametric and non-parametric rhythmometry, including those of Cristina herself, who deserves further credit for having first thought of long-term effects of betamimetics that were indeed documented and published by Elena V. Syutkina, the leader in chrononeonatology, with her active and productive team consisting of Alexander Grigoriev, Maria Mitish, Yuri Polyakov (who emigrated to the USA), and department head Prof. Galina Yatsyk. The team was enriched by the cooperation of Dr. Tamara Breus of the Space Science Institute and her associate Kirill Pimenov. The effect of distant drummers early in life remains a most challenging problem and the Moscow team is well-equipped to contribute toward its solution.

16. Moscow is the citadel of chronobiology and chronomedicine, thanks in substantial part to Prof. Rina M. Zaslavskaya, Chief of Cardiology at Moscow Hospital #60 and professor of therapeutics in Aktyubinsk, Kazakstan. There, the chronobiologist, now Professor, Kairgali Akhmetov is surrounded by younger colleagues such as Elena Petukhova, who used cosinor methodology to assess the merits of timing anti-anginal medications. The second Central Asian Congress on Cardiology in Almaty in September suggested that chronocardiology is alive and well, as do continuing major contributions by Kuniaki Otsuka, who demonstrated that CHAT in the absence of high blood pressure involves a very high risk of stroke. His finding now awaits extension to other populations by a truly chronotherapeutic approach, by optimizing both the self-hypnosis approach and medications by targeted timing as a follow-up on Yoshihiko Watanabe's and Takenori Kikuchi's contributions.

17. Steffen Klein, a physician and mentor of chronobiologic endeavors in his capacity as President of the International Society for Research on Civilization Diseases and the Environment, died in November. Dr. Klein's loss is acute. Before he died, he made a major contribution by proposing, endorsing and passing, in an international resolution, the 7-day monitoring up front of blood pressure and heart rate. In his memory, *secundum non datur*.

18. In keeping with the just-noted resolution, by invitation, Germaine, at a meeting in Ferrara in September 1995 of the New York Academy of Sciences, was critical of current blood pressure measurement practices. She showed, by simple computations, that (for most interesting cases), the office hour measurement of blood pressure can be equivalent to flipping a coin, should the 24-hour mean be 125/75 or 130/80 mm Hg and were one to follow the World Health Organization's recommendation to draw the limit of health at 140/90. Should there be a circadian amplitude of 20 mm Hg, which is near but still below the upper 95% prediction limit of healthy Caucasian adults, 42% of measurements will be above and of course 58% below these time-invariant arbitrary limits, at an average of 125/75, and 44% of the measurements will be above 140/90 when the mean is 130/80. Even the statement that in certain cases the 24-hour profile can be equivalent to the flip of a coin is not a vast exaggeration, but is documented on p. 35 of the resolution, which thus impeaches recommendations (on p. 34 thereof) by several national and international organizations. The task of chronobiologists is to properly qualify what others may regard as hyperbole, when the coin flip applies, to explain it in such simple terms that a discussion is superfluous.

19. This task is more difficult than was the endeavor in the 1950s to document rhythmicity in mammalian liver RNA and DNA and to find that RNA formation precedes DNA formation, at least in a given cycle, including a cycle which is started anew following partial hepatectomy. As Phil Regal put it, in a conversation, molecular evolutionists and chronobiologists can mutually enrich each other, for both can and should be concomitantly integrative as well as reductionist. The chronobiologic contribution stems from the fact that biochemistry in intact organisms is complex

and integrated by cycles rather than linearly. New analyses of old data serve to secure these facts in inferential statistical terms and were presented in Brno to honor the memory of Gregor Mendel.

20. Juan Roederer (Professor emeritus of Physics, University of Alaska, Fairbanks) visited us in March. We welcome his emphasis that our 1991 demonstration (in very large samples of myocardial infarctions) of effects from distant drummers (Bz turns) is now confirmed. We emphasize, as he does, that there is a less than 15% increase in adverse outcome associated with distant drummers and even this increase may at least in part be compensated for by a statistically significant decrease on the day following a Bz turn. We reiterate that by comparison in the sample of Kuniaki Otsuka's 297 patients, an excessive circadian blood pressure amplitude represents a relative risk of 8.2, a 720% increase in adverse outcome for the case of ischemic stroke. The by-comparison small geomagnetic effects were demonstrated in 1991 (Halberg F., Breus T.K., Cornelissen G., Bingham C., Hillman D.C., Rigatuso J., Delmore P., Bakken E., International Womb-to-Tomb Chronome Initiative Group: Chronobiology in space. University of Minnesota/Medtronic Chronobiology Seminar Series, #1, December 1991, 21 pp. of text, 70 figures) as part of an international chronome endeavor. Geomagnetic effects may be amplified when acting upon the organism's chronome, particularly upon components with nonsocietal about-half-weekly and -weekly patterns. To see if this is so, we hope to learn from friends in Moscow and Tyumen, Russia; Aktyubinsk, Kazakstan; Tokyo and if a new dean and extremely supportive associate vice-president for health sciences in Minnesota wish it, also in Minneapolis and St. Paul. There are chronobiologists everywhere, some of them in the position of Monsieur Jourdain (Moliere, *Le bourgeois gentilhomme*, Act II, Scene 4): "My goodness! For more than 40 years I spoke prose [chronobiology] without knowing it; and I am most obliged to you of all the people in the world for having told me so" ("Par ma foi! il y a plus de quarante ans que je dis de la prose sans que j'en susse rien, et je vous suis le plus oblige du monde de m'avoir appris cela.") They still believe that the analogy of some of our current practices with a coin flip is a vast exaggeration. They prefer the lamppost approach (Bypasser sees Simpleton on hands and knees under a lamppost one night: Bypasser: "What are you doing?" Simpleton: "Looking for my keys, I lost them under that bush over there." Bypasser: "But if you lost them under the bush, then why are you looking here under the lamppost?" Simpleton: "Because the light is better here!"). The lights are the casual measurement or the 24-hour profile. Both may be misleading if they are interpreted conventionally in light of fixed rather than chronobiologic reference values. The keys in the bushes are CHAT with or without MESOR-hypertension. To those who believe that borderline or mild hypertension can continue to be diagnosed as it is now, Table 1 of the resolution, the product of Germaine's background as a teacher, speaks for itself and can be recommended to health care providers worldwide.

With best wishes, also from Germaine, Mary and Denis,

Franz

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