Report of activities of the Halberg Chronobiology Center (HCC): 2016

Another year is coming to an end. As we reflect on work accomplished at the HCC, our thanks are extended to the many colleagues here and abroad who shared their energy and enthusiasm to make 2016 as productive as ever. Here are some highlights.

With Kuniaki Otsuka, Professor at Tokyo Women's Medical University's Executive Medical Center, Japan, work on the ECG monitoring of astronauts during long-term missions on the International Space Station continued. After showing that the fractal scaling of the long-term heart rate variability (HRV) experienced significant and consistent disruption under microgravity conditions, we found that this lasting disruption of the HRV occurred primarily in a frequency region centered around one cycle in about 90 minutes, Kleitman's BRAC (REM/NREM) cycle. Results have just been published online in the new journal "Heliyon".

Also with Professor Otsuka, joint results based on around-the-clock monitoring of blood pressure and the ECG, obtained over the past 3 decades, have been published in a book on chronomics published by Springer. The 870 plus page-book summarizes findings from past and still ongoing investigations of cardiovascular disease risk associated with alterations in the variability of blood pressure and heart rate. It also addresses how blood pressure and heart rate variabilities are affected by changes in the terrestrial, solar and cosmic environment. The book includes the latest works by Professor Franz Halberg that were still unpublished at the time of his death.

With Jarmila Siegelova, Professor at Brno's Masaryk University, Czech Republic, and her team, we revisited changes in the time structure of blood pressure and heart rate as a function of age. Her Brno database of 7-day/24-hour ABPM was well-suited to examine the variance transposition from the circadian domain to both ultradians and infradians, components with periods shorter or longer than 24 hours, respectively. The most striking finding was the large incidence of individuals who had a circadian period deviating with statistical significance from 24 hours. With Shahrukh Rizvi, a graduate student in our physiology department, these findings are now being compared between study participants who were or were not taking anti-hypertensive medication. Results on the Brno database were presented at the yearly meetings on Noninvasive Methods in Cardiology organized by Professor Siegelova, where we also reviewed how blood pressure monitoring changed since the first records obtained with an Arteriosonde in the mid-1970s as part of our International Breast Cancer Risk Study. Our work on the chronobiology of aging earned Germaine the invitation from the journal "Gerontology" to publish a mini-review of the field.

With Dr. Ram B Singh, Professor at the Halberg Hospital and Research Institute in Moradabad, India, we continue as editors of the World Heart Journal. As evidenced from this year's publications listed below, several papers and editorials sought to bring awareness of chronobiologic principles as they relate to the fields of cardiology and nutrition. As in past years, the June issue was dedicated to the memory of our mentor, Franz Halberg.

Our project on the BIOsphere and the COSmos (BIOCOS) is as strong as ever: ABPM records, mostly over 7 days, continue to accumulate, notably from investigators in Belgium, the Czech Republic, India, and Japan, thanks to support from the A&D Company (Tokyo, Japan). We are indebted to the volunteering IEEE engineers of the Phoenix Project for exploring alternative noninvasive techniques to measure blood pressure; new technological advances are exciting as they offer both new ideas and new challenges.

Within BIOCOS, in cooperation with RK Singh, Professor of Biochemistry at the Shri Guru Ram Rai Institute of Medical & Health Sciences, Patel Nagar, Dehradun, and with his daughter Ranjana Singh, Associate Professor of Biochemistry at King George's Medical University, Lucknow, the effect of diet and smoking status on circadian rhythm characteristics of circulating plasma lipid components was examined in healthy Indians of both genders and different age groups. Omnivores were found to have higher total cholesterol concentrations than vegetarians, as did smokers as compared to non-smokers. We also compared circadian rhythms of circulating plasma lipid peroxides, uric acid and ascorbic acid between renal stone formers and matched healthy controls. By comparison to the healthy controls, stone formers had an elevated malondialdehyde, a lower serum ascorbic acid, and similar values of serum uric acid. The patients also differed from the healthy subjects in terms of their circadian amplitude and phase of all three variables. Upon invitation from Dr. RB Singh and Dr. Fabien De Meester, Founder of the TsimTsoum Institute, Krakow, Poland, we reviewed the chronobiology of cholesterol in a chapter of Fabien's new Handbook of Cholesterol: Biology, Function and Role in Health and Diseases.

With Denis Gubin, Professor at Tyumen's Medical University, Siberia, we examined about-daily (circadian), about-weekly (circaseptan), and about-yearly (circannual) incidence patterns of adverse cardiovascular and cerebral events, recorded from emergencies resulting in a call for an ambulance in Khanty, Siberia. With Tony Tran, an undergraduate student in physiology and computer science at our University, we are further investigating how these incidence patterns are affected by environmental conditions, such as air temperature and atmospheric pressure, and whether any such influences are more pronounced in the elderly.

With Lyazzat Gumarova, Associate Professor at Al-Farabi Kazakh National University, Almaty, Kazakhstan, we completed our analysis and review of tropical malaria incidence, finding that transyears (components with a period of about 1.3 years similar to that found in solar wind speed) compete with the seasons. Thanks to Borislav Dimitrov, Associate Professor in Medical Statistics at the University of Southampton, United Kingdom, the results are now published in a chapter of a book on "Current Topics in Malaria" just off the press. We are very happy and proud that Lyazzat was just awarded a best teacher award from her country. She plans on implementing some of her proposed work with us next summer.

Cooperation continued with Weihong Pan, Professor at Pennington Biomedical Research Center, and now Medical Director of the Biopotentials Sleep Center in Baton Rouge, Louisiana. Results from our study of how sleep fragmentation blunts the circadian variation of autophagy in mouse hippocampus have been published in Chronobiology International.

Elizabeth Lusczek, Associate Professor in our University's Department of Surgery, completed the data collection of her pilot study aimed at monitoring circadian rhythms of vital signs and metabolomics in healthy people and in patients admitted in the intensive care unit. We just started analyzing the data in preparation for her grant application to NIH. This feasibility study will serve as a reference for assessing planned interventions to strengthen the circadian system of patients with the aim to improve outcomes such as reducing the length of hospitalization and the incidence of complications. EEG monitoring was added to the protocol this year, in cooperation with Umesh Goswami, Assistant Professor of Medicine. Both Beth and I volunteered to test overnight the Sleep Profiler used for monitoring the EEG: the about 90-minute REM/non-REM cycle was striking in each case.

At the HCC, Cathy Lee Gierke's "Chronomics Analysis Toolkit (CATkit)" program has attracted interest by several investigators nationally and internationally. She continues to perfect the program's output and added new graphic illustrations of the results. The program is currently being beta-tested by Miguel Revilla, Professor of Applied Mathematics at the University of Valladolid, Spain, and by Dr. Douglas Wilson, Statistician at the College of Human and Health Sciences in Swansea, Wales, before it is submitted to CRAN. Cathy illustrated the use of her program at the meeting in Brno, as she applied it to study the effect of transmeridian travel on the circadian rhythm of locomotor activity, to determine major periodic components in the incidence of adverse cerebro-cardiovascular events, and to assess their circadian waveform by multi-component modeling. With Cathy, we also examined how the circadian rhythm characteristics of circulating melatonin change as a function of age, using data originally collected with the late Professor of Internal Medicine at the University of Florence, Italy, Brunetto Tarquini, and his team in Florence, Italy. The expected decrease in circadian amplitude with increasing age was corroborated, but the new finding was a slight rebound at very old ages, notably in women, a reminder of the difficulty to separate effects of healthy aging from those of impending disease, and of the merits of longitudinal (lifelong whenever possible) monitoring. Cathy presented these results at the second meeting of the Indian Society for Chronomedicine held in Lucknow, India, in October 2016.

We are happy to have Mary Sampson back at the lab after a long absence of several months. Linda Sackett-Lundeen, Medical Technologist, has recently joined the HCC team to work on the "Atlas of Chronomes" in cooperation with Software Engineer Larry Beaty, Cathy, and Germaine. As a seasoned experienced chronobiologist, Linda is uniquely qualified to bring this long-term project to fruition.

The HCC keeps attracting visitors. Continuing a long-term tradition, Yoshihiko Watanabe, Professor of Internal Medicine at Tokyo Women's Medical University, Japan, came to work with us to optimize the administration of several anti-hypertensive drug combinations by timing. In addition to the individualized chronotherapy of new drug combinations, we are also assessing the extent of reproducibility of optimal treatment times and any confounding by the circannual modulation of the circadian pattern of blood pressure. This year, Yoshihiko also brought data examining the effect of finger acupressure on blood pressure. To the known therapeutic effect to relieve pain, Yoshihiko demonstrated an anti-hypertensive effect on 3 patients. While the sample size is still very small, the results suggest that acupressure may also alleviate some of the vascular variability disorders in addition to lowering blood pressure.

We had the pleasure to see Drs. Francine Halberg and Terry Kessler in June. It was an opportunity to pause and review work accomplished thus far and discuss tasks ahead. We had the opportunity to meet with the University archivist who may organize materials related to Franz's legacy. We also had the visit of Bing Wu, the son of our former colleague Professor Jinyi Wu from Chengdu, PR China. Bing, who founded the ChronoCloud Company in Shanghai, intends to branch out to the Twin Cities. He brought with him his latest prototype of an ambulatory blood pressure monitor that consists solely of an arm cuff. While more comfortable than usual ABPM devices, it does not yet have a display, but it speaks out the measurements … in Chinese. We are looking forward to further interactions with Bing once proper arrangements can be made that meet our University's regulations.

Many more projects are ongoing. With James Wanliss, Professor of Physics at Presbyterian College in Clinton, South Carolina, the extensive around-the-clock blood pressure and heart rate data collected by Franz Halberg over some 25 years have been examined by superposed epoch analysis to test for possible space weather connections, results still awaiting publication. With Tom Kazlausky, President of Ambulatory Monitoring Inc., we are investigating the circadian variation in locomotor activity and how it changes over time in year-long longitudinal records. With Banshi Saboo, experienced Physician specializing in Diabetes in Ahmadabad, India, we are learning about glucose variability in diabetic patients. With Dr. Pavel Homolka, Physician at Masaryk University in Brno, Czech Republic, we are monitoring the blood pressure and heart rate of patients with normal-weight obesity. With Anna Gvozdjakova, Professor at Comenius University, Bratislava, Slovakia, we learn about circadian rhythms' involvement in mitochondrial medicine. With Mutlu Gur, Associate Professor at Ahi Evran University, Kirsehir, Turkey, we are analyzing temperature data from ground squirrels before, during and after hibernation. Two grant applications have been submitted to the ISTC in cooperation with the HCC: one by Lyazzat on environmental influences on blood pressure; the other by Ketevan Janashia, Project Manager at the Helio-Magneto-Cardiological Scientific and Practical Centre in Tbilisi, Republic of Georgia, to study the influence of geomagnetic field disturbances on the autonomic regulation of healthy magnetosensitive humans, in preparation for long-term space exploration.

Work at the HCC was in the spotlight. The Atlantic published a 4-page article, emphasizing the importance of our work on longitudinal monitoring. We introduced the vascular variability disorders at a meeting on stroke organized by the Minnesota Department of Health and held in the Twin Cities. We were invited to present (by Skype) our work on aging at the Brno workshops organized by Jarmila and in person at the International Conference on Chronomedicine in Lucknow, India. With Dr. Yury Gurfinkel, Research Department Head at the Space Research Institute, Russian Academy of Sciences, and The Research Clinical Center of JSC "Russian Railways", in Moscow, Russia, and with Dr. Tamara Breus, Physicist at the Space Research Institute, Russian Academy of Sciences, in Moscow, Russia, Germaine's ePoster on the influence of space weather on heart rate and heart rate variability was presented at the 13th European Space Weather Week in Oostende, Belgium. Posters prepared by Shahrukh Rizvi and Tony Tran, physiology students working at the HCC, were presented at the yearly CardioPalooza venue organized by the Department of Integrative Biology and Physiology and the Lillehei Institute. Germaine was invited to join the Editorial Board of Perceptual Motor Skills, now published by SAGE.

Mary Sampson and Cathy Lee Gierke are maintaining and updating our website. Please visit us at http://halbergchronobiologycenter.umn.edu where you can meet our key collaborators, download some tutorials on chronobiology and see recently published titles. You will also find the full bibliography of Franz Halberg along with his curriculum vitae, interviews he gave, an autobiography, and a page illustrating his life in pictures.

The HCC continues to benefit from cooperation with many more colleagues locally, nationally, and internationally. In particular, we are grateful to Drs. Francine and Julia Halberg who serve as advisors to the HCC. Their continued support of activities at the HCC is much appreciated.

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