

Another pandemic year has passed. Despite many challenges, we are grateful for the continued activities at the Halberg Chronobiology Center, performed mostly remotely from home. We thank all our colleagues here and abroad for the opportunity of further cooperation. Below are some highlights of this year's achievements.

The focus of the Center remains centered on the monitoring of blood pressure in health and disease and on changes in the time structure of heart rate variability and activity in astronauts during long missions on the International Space Station (ISS).

Work with Kuniaki Otsuka, Professor at Tokyo Totsuka Royal Clinic, Women's Medical University's Executive Medical Center, Japan, in cooperation with members of the Japanese Space Agency, focused on 48-hour ECG monitoring of astronauts during long-term (about 6-month) missions in space, complemented by actigraphy. Our results showing that the circadian rhythm of heart rate strengthened in space and that sleep quality improved were published in *Scientific Reports*. The data suggest that magnetic fluctuations may mediate these effects. Other work with Kuniaki showed that lifestyle interventions to improve arterial compliance and prevent frailty in the elderly should be therapeutic targets to delay or prevent the onset of dementia in community-dwelling citizens.

Thanks to support from the A&D Company (Tokyo, Japan), our project on the BIOSphere and the COSmos (BIOCOS) continues in several countries, notably in Brno, Czech Republic, Tokyo, Japan, and Brussels, Belgium. While wrist-worn blood pressure devices are still not sufficiently accurate for automated longitudinal monitoring, they are sparking much interest, and warrant further testing in cooperation with El Nolley, Chris Adams, and Larry A Beaty, volunteering IEEE engineers of the Phoenix Project. Information regarding rest-activity is an added feature in the new ABPM model from A&D. The circadian variation of blood pressure was compared to that of locomotor activity in a group of young, clinically healthy individuals in cooperation with Lyazzat Gumarova, Associate Professor of Biophysics at Al-Farabi Kazakh National University, Almaty, Kazakhstan. The results confirm that both variables show a strong common circadian variation and that blood pressure is not a sole direct response to the circadian rhythm of physical activity. These results were published in *Biological Rhythm Research*.

As a complementary approach to ABPM, work with Larry Beaty is proceeding to analyze beat-to-beat blood pressure waveforms recorded over a few minutes within the MESA project. David Jacobs, Professor of Epidemiology, and Daniel Duprez, Professor of Cardiology, both at the University of Minnesota, showed that the characterization of features of the blood pressure waveform is predictive of cardiovascular disease risk. Now that we streamlined existing R code to analyze the data automatically, we are developing new algorithms to improve the identification of markings corresponding to specific events that occur within a cardiac cycle. Results are discussed in monthly meetings with Matthew Allison, Professor of Public Health, University of California, and his team, in the context of an ongoing NIH-funded project.

With Denis Gubin, Professor at Tyumen State Medical University, Russia, research on open-angle glaucoma proceeded by investigating effects of long-term administration of melatonin in these patients. Melatonin supplementation was found to increase the stability of the circadian rhythm in body temperature by improving its phase alignment and the alignment with the rhythm in intra-ocular pressure, and to improve the function of retinal ganglion cells (RGCs) in advanced glaucoma. In a

follow-up study of these patients, we found that depression scores were strongly associated with RGCs loss in glaucoma, supporting the hypothesis that RGCs loss in advanced glaucoma may affect non-visual photic transduction and lead to mood disturbances.

The World Heart Journal published long abstracts presented at the International Conference on “Chronobiology in Medicine and Sport”, organized by Friendship’s University of Russia in Moscow, which was dedicated to the 100th anniversary of the birth of Franz Halberg, held virtually on December 7-9, 2020. Several joint projects were presented at the meeting. In cooperation with Jarmila Siegelova, Professor at Masaryk University, Brno, Czech Republic, we showed that a cosinor analysis of ABPM data interpreted in the light of chronobiologic reference values led to better reproducible results and a more accurate diagnosis than a computation of the day-night ratio of blood pressure for a classification in terms of dipping.

On October 13, Jarmila held her annual Workshop on Noninvasive Methods in Cardiology. Ten years after his premature death, we paid homage to the late Bohumil Fiser, Professor and Head of the Department of Physiology at Masaryk University, who was Minister of Health of the Czech Republic from 2000 to 2002. In his honor, the HCC delivered three presentations, including work with A. Chase Turner, retired Software Engineer who demonstrated cosinor-based applications he implemented in Mathematica. Colette Sandborgh, an undergraduate student in the Department of Integrative Biology and Physiology at the University of Minnesota, who is working on a research project at the HCC, compared the circadian variation in circulating cortisol of clinically healthy women studied in different stages of the menstrual cycle. While there were no differences in circadian characteristics, she is now analyzing the pulsatile behavior of cortisol. The third lecture reviewed earlier work on circadian disruptions in leptin and blood pressure in relation to obesity.

At the HCC, we are still all working remotely. Mary Sampson adapted quickly to work from home on her new laptop. With Linda Sackett-Lundeen, she continues to work on the bibliography of Franz Halberg by listing a number of keywords associated with each publication. She has also taken on the responsibility of keeping us informed about newly published works in chronobiology. Her continued help with editing papers for the World Heart Journal is invaluable. Linda, who is in charge of assembling the entire bibliography of Franz in both searchable electronic form and hard copies, is completing the first decade of the 21st century. Just a few more years to complete the task! Linda is also helping with data analysis and discussions with the students. She revived most of the database from our breast cancer study. Data on cortisol were particularly helpful to colleagues in the Medical School interested in the treatment of children with congenital adrenal hyperplasia. Cathy Lee Gierke, who retired last year, has maintained contact and is currently expanding her CATkit program to include a polar display of cosinor results.

Weekly lab meetings held by Zoom have been productive. In particular, much progress has been achieved by Chase to use Mathematica for chronobiologic analyses, including the nonlinear least squares estimation of multi-frequency models. Chase initiated direct discussions with key personnel at Wolfram to solve some of the issues encountered in the process. In relation to all ongoing projects, we continue to benefit from the expertise of and advice from Larry. The automatic non-invasive, cuff-less monitoring of blood pressure remains one of several topics of interest.

Several students came to work on research projects with us. Colette analyzed cortisol data for their circadian rhythm and pulsatile behavior. Jessica Llapa learned about the merits of personalized chronotherapy by re-analyzing some of the data from Yoshihiko Watanabe, emeritus Professor of

Internal Medicine at Tokyo Women's Medical University, Japan. Several students also came to the HCC to write their capstone. Rachel Staaden reviewed the effect of clock genes on ovulation. Zach Faith was interested in the involvement of circadian disruption in depression. Mason Hayden focused on the pineal gland. His selection of a publication on single-cell sequencing of the pineal gland documented the existence of two distinct populations of pinealocytes with cell-specific time-of-day dependent changes in gene expression.

Work at the HCC attracted several invitations. Wojciech Krzyzanski, Professor at the State University of New York at Buffalo, NY, USA, Associate Editor of the Journal of Pharmacokinetics and Pharmacodynamics, invited Germaine to publish a paper in a Special Issue of the journal on Chronopharmacometrics, where she reviewed cosinor and other time series analysis techniques used in chronobiology. As member of the Presidium of the International Academy of Science (IAS), she was also invited to write an Introduction to Chronobiology, which was published in the Society's journal, the Herald. The IAS' President, Walter Kofler, Professor of Ecology at the University of Innsbruck, Austria, with whom we had several email discussions to exchange ideas, reviewed means to fight the SARS-CoV-2 virus in a special issue of the Herald. This year, Germaine joined the Editorial Board of Clinical Interventions in Aging (IF=2.651) and the International Journal of Environmental Research and Public Health (IF=3.390).

The possibility to lecture remotely was particularly attractive, as it enabled Germaine to accept multiple invitations to participate at international meetings. Among others, she was invited to talk about rhythm alterations as sensitive gauges of aging and cardiovascular disease as a CME course in Dubai, UAE, at the 10th International Congress of Cardiology & Cardiovascular Imaging held March 26-27, 2021. Also as a CME course in Dubai, UAE, she talked about circadian alterations in the presence of diabetes at the 10th International Congress of Cardiology and Diabetes, held October 29-31, 2021. On March 24, 2021, she was invited to talk about chronobiology in the context of a meeting on personalized medicine held in Lucknow, India. She was invited to report on circadian alterations in obesity at the 8th Central European Congress on Obesity, held virtually on October 7-8, 2021. On November 26, 2021, she gave the opening lecture on the history of chronobiology at the Coherence 2021 meeting in Rome, Italy.

This year, with great sadness, we mourn the loss of Dr. Hugh Simpson, Professor in the Department of Pathology at the University of Glasgow, Scotland. We remember his work on breast cancer in a forthcoming issue of the World Heart Journal. We also mourn the loss of Dr. Dewayne Hillman, a long-standing member of the HCC and a dear colleague who was an integral part on our journey of chronobiologic research and discovery.

The HCC continues to benefit from cooperation by 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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