

Another year has gone by. As we reflect on activities at the Halberg Chronobiology Center, we thank all our colleagues and friends here and abroad for the continued success of the Center.

The year 2019 marked the 100th anniversary of the birth of Franz Halberg. While our plans for a special lecture had to be postponed due to unforeseen circumstances, Franz was honored at several international meetings to which we had the honor to contribute. A special tribute to him had already been delivered in May 2018 at the occasion of the 25th anniversary of the Russian Section of the International Academy of Sciences (Health and Ecology). Halberg's centenary was also commemorated this past year in the first issue of the new "Journal of Chronomedicine" together with its editor-in-chief, Denis Gubin, Professor at Tyumen's Medical University, Siberia. This institution indeed decided to develop its former "Tyumen Medical Journal" in the direction of chronobiology and chronomedicine. The lifetime achievements of Franz were further highlighted, first in Graz, Austria, at a meeting organized by Nandu Goswami, Interim Head of the Division of Physiology at the Otto Loewi Research Center, and later in Brno, Czech Republic, at the annual Workshop on Noninvasive Methods in Cardiology organized by Jarmila Siegelova, Professor at Masaryk University. On July 3-5, 2019, while in Minnesota some of us fondly remembered Franz over dinner and discussed the future direction of his Center at the University of Minnesota, the International Society for Chronobiology held its 30th International meeting in Warsaw, Poland. While its former President, Professor Francesco Portaluppi, had agreed to present a few slides highlighting the history of the Society and the critical role Franz Halberg played in its early years, our lecture and those of several other speakers were also dedicated to Franz. Next February, Halberg's work will be celebrated in the opening lecture by Germaine at a meeting of chronobiology in St. Petersburg, Russia, organized by Mikhail Blank, Professor at the Russian Research Center for Radiology and Surgical Technologies.

As in previous years, The HCC was as active and productive as ever, thanks to cooperation with colleagues locally, nationally, and internationally. The focus of the Center remains centered on the around-the-clock monitoring of blood pressure and other physiological functions on Earth and in space. Lessons learned regarding alterations in the circadian variation of blood pressure associated with cardiovascular disease risk are being investigated in other domains, both at the organismic level and at the molecular and cellular levels. Selected highlights are detailed below.

The space environment is both fascinating and posing interesting challenges. Reports that aging may slow down in space prompted our further investigation of ECG data of astronauts during long-term missions on the International Space Station. This project 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, highlighted the role of magnetic changes in the magnetosphere in affecting and enhancing indices of heart rate variability in space. We published in Scientific Reports our finding that they may convey an anti-aging effect in association with the brain's default mode network, and in a light- and/or circadian stage-dependent manner. Plans are also being made to explore effects of microgravity and magnetic disturbances on skin growth in space with Mei and Paul Bigliardi, Professors in the Department of Dermatology at the University of Minnesota. It has indeed been described that astronauts returning from long-term space trips have unexplained and particular skin disorders.

The Quantum Self revolution has spurred much interest in continuous monitoring of physiological functions. Despite efforts by several companies to develop cuff-less blood pressure devices based on photo-plethysmography, the accuracy and reliability of this approach remain lacking. Our efforts with El Nolley, Chris Adams, and Larry A Beaty, volunteering IEEE engineers of the Phoenix Project, to keep exploring alternative noninvasive techniques to measure blood pressure are thus as much in the forefront as ever. In particular, we are considering modifications of cuff-based wrist monitors, now widely used for manual home monitoring, to render them truly ambulatory. In the interim, ambulatory blood pressure monitors (ABPMs) continue to be used in several geographic locations as part of our Project on the BIOSphere and the COSmos (BIOCOS), thanks to support from the A&D Company (Tokyo, Japan).

Our study of the new guidelines from the American College of Cardiology and the American Heart Association, as well as from the European Society of Cardiology and the European Society of Hypertension, regarding the use of ABPM indicated two reasons for their limited recommended use. One was limiting monitoring to 24 hours, and the other relying only on the computation of daytime, nighttime, and 24-hour mean values. Accordingly, this year, we analyzed two large databases of 7-day/24-hour ABPM records to compare the relative merits of this conventional approach in terms of “dipping” to our chronobiologic approach, which relies on modeling the data to assess their circadian variation. With Linda Sackett-Lundeen and Mason Voth, an undergraduate student from our department of Integrative Biology and Physiology, we documented the merit of monitoring for longer than 24 hours by assessing the extent of day-to-day variability in all circadian parameters in the presence or absence of hypertension. We also showed that even when ABPM is restricted to 24 hours, a chronobiologic diagnosis is more reliable (less variable from one day to another) than a diagnosis based on the day-night ratio.

As a complementary approach, the characterization of features of the beat-to-beat blood pressure waveform recorded over minutes or at most a few hours is also informative, as illustrated in epidemiological studies by David Jacobs, Professor of Epidemiology, and Daniel Duprez, Professor of Cardiology, both at the University of Minnesota. As part of their project to assess the relation of these blood pressure waveform features to cardiovascular risk, with Software Engineer Larry A Beaty, we streamlined existing R code to automatically analyze the data and are currently working on extending the work to the analysis of additional databases.

The HCC hosted several international visitors this year. To continue a long tradition, Yoshihiko Watanabe, emeritus Professor of Internal Medicine at Tokyo Women’s Medical University, Japan, returned for weeklong visits to Minnesota in January and September. With him, the personalized optimization of anti-hypertensive treatment by timing continued. The protocol of repeated 7-day/24-hour ABPM profiles when the same dose of the same medication is administered to the same patient at different circadian stages in relation to the time of awakening was extended from the original Hyzaar treatment to other drug formulations. Our work shows the importance of determining the best time to treat for each individual patient, even if on the average, outcomes may be improved overall by treating everybody indiscriminately in the evening, since such a strategy is likely to harm some patients with distinct abnormalities of their blood pressure variability. Merits of personalized chronotherapy were illustrated in a case report of a patient with aldosteronism treated with spironolactone published with Hyunyong Kim, a former student of our department who helped with data analysis.

Within the scope of her 3-year grant, Lyazzat Gumarova, Associate Professor at Al-Farabi Kazakh National University, Almaty, Kazakhstan, came to spend part of the summer in Minnesota. It was an opportunity to revisit work done by Zainab Farah, a former student from our department on 7-day/24-hour records of blood pressure and locomotor activity to compare their circadian patterns. Contrary to the widespread belief that changes in blood pressure follow changes in activity, no differences were found in the circadian phase of these variables, a finding now being prepared for publication. During her stay, we analyzed her new data on the effect of altitude on blood pressure. In addition to the anticipated increase in blood pressure at a higher altitude, we found that the increase in blood pressure was larger among participants with a higher blood pressure at the outset. Lyazzat presented these results in a poster at our department's annual CardioPalooza event.

In the middle of an unusually frigid and very snowy winter, we hosted Fernanda Gaspar do Amaral, Professor of Physiology at Federal University of São Paulo, who came to become more familiar with our methods of data analysis. As an expert on the pineal gland and melatonin, we analyzed some of the data she brought with her, and discussed ongoing and future work, including alterations in the circadian rhythm of melatonin in the presence of diabetes. She had a great opportunity to participate at a Journal Club meeting of our department of Endocrinology where her work was discussed.

Results from several ongoing projects have been published this year. A small study on time restricted feeding conducted by Ram B Singh, Professor at the Halberg Hospital and Research Institute in Moradabad, India, replicated findings originally made by Franz Halberg over 40 years ago. Specifically, we found that eating in the evening can predispose to obesity, central obesity and increases in fasting blood glucose and Hb1c that are indicators of the metabolic syndrome; by contrast, eating in the morning can decrease Hb1c and systolic blood pressure, indicating that it may be protective against the metabolic syndrome. Results have been published in *Chronobiology International*. With Jarmila Siegelova, we carried out another small case-control study to examine the effect of shift work on the circadian rhythm of blood pressure. Confirming earlier results, we found that shift work is associated with an elevated blood pressure and that night shift is associated with a damping of the circadian amplitude of blood pressure. Work on open-angle glaucoma continued under the leadership of Denis Gubin. With him, we found that the circadian rhythm of intraocular pressure had an inverted phase in patients with an advanced condition but not in patients with a stable condition. These recent results have been submitted for publication. Results from a pilot study with Elizabeth Luszczek, Assistant Professor in the department of Surgery at the University of Minnesota, on circadian rhythms of vital signs and metabolomics in patients admitted to the Intensive Care Unit are currently in press. In addition to the desynchronization of circadian rhythms observed in ICU patients compared to healthy controls, clustering of plasma metabolic profiles suggests that metabolomics could be used to track individual patients' clinical courses longitudinally.

At the HCC, Mary Sampson continues to help edit manuscripts, notably for the *World Heart Journal*. She also helps Linda Sackett-Lundeen with assembling and scanning the entire bibliography of Franz Halberg. With over 3,600 published titles, this represents a slow process, but a worthwhile endeavor since it will eventually lead to a fully searchable electronic database. Linda is also involved in a number of other projects, from literature reviews to data analyses. Cathy Lee Gierke added to her CATkit program the "plexogram", a data analysis procedure used to visualize the waveform of a given periodicity and to test its statistical significance. An updated version of CATkit was uploaded to CRAN to make all programs freely available. Since the "plexogram" is a

relatively simple method, it was a good opportunity for Cathy to write this program also in R Shiny, an R-based environment enabling a graphical user interface and interactive use of the program on the web. The R Shiny plexogram is available at <https://catkit.shinyapps.io/ShinyCATkit/>. Several students came to the HCC to do their capstone. Their topics varied from the monitoring of locomotor activity and the effect of shift work on metabolic disease to the bidirectional effects of diabetes mellitus and circadian rhythm dysfunction and the role of circadian rhythms of microglia in neuroinflammation. The HCC benefitted from much work and advice from Larry A Beaty and from A Chase Turner. With them, we are learning how to use Mathematica and how to retrieve data from an Apple watch in preparation for an Apple's ResearchKit application to study the effect of space weather on heart rate variability.

Work at the HCC attracted several invitations to lecture and other distinctions. Germaine was invited by Professor Abdullah al-Abdulgader to participate in the 5th International Conference for Advanced Cardiac and Heart Transplant (King of Organs 2019), organized by the Prince Sultan Heart Center in Al-Ahsa, in collaboration with the Cardiology Center at the Hospital La Salpetriere in Paris, held on March 24-27, 2019. Her videoconference was well received and earned her the invitation to contribute a follow-up paper in Heart and Mind published by Wolters Kluwer-Medknow. On June 17, Germaine gave the after-dinner talk celebrating the 100th anniversary of the birth of Theodor Hellbrügge, chronobiologist and founder of the discipline of social pediatrics, by invitation from his daughter Petra. The 2-week historic event of 50 years of Montessori Inclusion Practice took place in Milwaukee, Wisconsin, presented by the Theodor Hellbrügge Foundation and sponsored by Montessori Medical Partnership for Inclusion and Penfield Children's Center/ Penfield Montessori Academy. Theodor Hellbrügge, a life-long friend of Franz Halberg, had collaborated with Mario Montessori in the 1970's to reconnect his mother's work with the science of developmental rehabilitation to create an inclusive Montessori education. In April, Germaine was interviewed by Ira S Pastor, host of ideaXme regarding work done at the HCC on aging and longevity. The ~45-minute interview is posted on the HCC website and can be viewed at <https://www.youtube.com/watch?v=BxQUAKNGw-M>. At the October 8 meeting of the General Assembly of the International Academy of Science held in Nicosia, Northern Cyprus, Germaine was elected to its Presidium for the 2019-2022 term to represent North America.

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.

Germaine Cornelissen
Professor, Integrative Biology and Physiology
Director, Halberg Chronobiology Center
Coordinator, Project on the BIOSphere and the COSmos (BIOCOS)
corne001@umn.edu
<http://halbergchronobiologycenter.umn.edu>

1. **Cornelissen G**, Watanabe Y, Siegelova J, Turner AC, Beaty L, Otsuka K. Importance of chronotherapy protocols in chronomedicine. In: Chibisov SM, Rapoport SI, Blagonravov ML (Eds.) *Chronobiologiya i Chronomeditsina: monografiya*. Moscow: People's Friendship University of Russia 2018; 473-500.
2. **Cornelissen G**, Sackett Lundeen L, Lee Gierke C, Sampson M, Turner AC, Beaty LA. Season's appreciations: activities at the Halberg Chronobiology Center in 2018. *Herald of the International Academy of Sciences. Russian Section* 2019; 1: 75-81.
3. **Cornelissen G**, Watanabe Y, Siegelova J, Beaty LA, Singh RK, Singh R, Singh RB, Delcourt A, Gumarova L, Gubin D, Chen CH, Otsuka K, for Investigators of the Project on the BIOSphere and the COSmos (BIOCOS) and Members of the Phoenix Study Group. Chronobiologically interpreted ambulatory blood pressure monitoring: past, present, and future. *Biological Rhythm Research* 2019; 50 (1): 46-62.
4. Singh RB, Hristova K, Fedacko J, El-Kilany G, **Cornelissen G**. Chronic heart failure: a disease of the brain. *Heart Failure Reviews* 2019; 24 (2): 301-307.
5. Gubin DG, Malishevskaya TN, Astakhov YS, Astakhov SY, **Cornelissen G**, Kuznetsov VA, Weinert D. Progressive retinal ganglion cell loss in primary open-angle glaucoma is associated with temperature circadian rhythm phase delay and compromised sleep. *Chronobiology Int.* 2019; 36 (4): 564-577.
6. Sletten J, Lund A, Ebbing C, **Cornelissen G**, Aßmus J, Kiserud T, Albrechtsen S, Kessler J. The fetal circadian rhythm in pregnancies complicated by pregestational diabetes is altered by maternal glycemic control and the morning cortisol concentration. *Chronobiology Int.* 2019; 36 (4): 481-492.
7. Gumarova L, Gumarova Z, **Cornelissen G**. Influence of BMI on cardiovascular circadian rhythms of young adults. *World Heart J* 2019; 11 (1): 49-56.
8. Watanabe Y, Kim H, **Cornelissen G**. Spironolactone chronotherapy of hypertensive patient with aldosteronism: case report. *World Heart J* 2019; 11 (1): 57-63.
9. Sackett Lundeen L, **Cornelissen G**. Amplification on "Cortisol and the heart". *World Heart J* 2019; 11 (2): 123-128.
10. **Cornelissen G**. 100th anniversary celebration of the birth of Franz Halberg. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2019*. Masaryk University, Brno, Czech Republic 2019; 11-15.
11. **Cornelissen G**, Havelkova A, Lee Gierke C, Sackett Lundeen L, Siegelova J. Effect of shift-work on the circadian rhythm of blood pressure. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2019*. Masaryk University, Brno, Czech Republic 2019; 31-40.
12. Sackett Lundeen L, Havelkova A, Beaty LA, Voth M, Siegelova J, Otsuka K, **Cornelissen G**. Day-to-day variation in day-night ratio of blood pressure. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2019*. Masaryk University, Brno, Czech Republic 2019; 41-49.
13. Siegelova J, Havelkova A, Krabkova M, Dusek J, Pohanka M, Dunklerova L, Dobsak P, **Cornelissen G**. Seven-day/24-h ambulatory blood pressure monitoring in night shift workers: excessive pulse pressure. In: **Cornelissen G**, Siegelova J, Dobsak P (Eds.) *Noninvasive Methods in Cardiology 2019*. Masaryk University, Brno, Czech Republic 2019; 57-66.
14. Singh RB, Watanabe S, Li D, Nakamura T, Juneja LR, Takahashi T, Maheshwari A, Verma N, Wichansawakun S, **Cornelissen G**, Wilczynska A, Jantan I, Sulaeman A, Ridwan H, Manan WA, Mojto V, Kartikey K. Diet and lifestyle guidelines and desirable levels of risk factors and protective factors for prevention of dementia: a scientific statement from the joint symposium of

- JASS and APCNS. Biomedical Journal of Scientific & Technical Research 2019; 17 (3): 12844-12864.
15. Singh R, Kumar P, Mishra DN, Singh AK, Singh RK, Mahdi AA, Gierke CL, **Cornelissen G**. Effect of gender, age, diet and smoking status on the circadian rhythm of serum uric acid of healthy Indians of different age groups. *Indian J Clin Biochem* 2019; 34 (2): 164-171.
 16. Otsuka K, **Cornelissen G**, Kubo Y, Shibata K, Mizuno K, Ohshima H, Furukawa S, Mukai C. Anti-aging effects of long-term space missions, estimated by heart rate variability. *Scientific Reports* 2019; 9: 8995. DOI <https://doi.org/10.1038/s41598-019-45387-6>
 17. Watanabe Y, Otsuka K, **Cornelissen G**, Halberg F. Personalized blood pressure chronotherapy. In: *Transactions of the International Academy of Science H&E* 2017-2019; 4: 59-65.
 18. Otsuka K, **Cornelissen G**, Yamanaka G, Kubo Y, Kikuchi T, Murakami S, Sasaki J, Saito Y. Combination assessment of ToCA-MCI and Cardio-Ankle Vascular Index (CAVI) is useful for early detection of amnesic MCI in elderly Japanese citizens. In: Orimo H, Shirai K, Takata M et al., eds. *CAVI and Neuro-Cardiovascular Function*, 1st Ed. Tokyo: Vascular Health Promotion Society 2019; 80-86.
 19. Singh RB, **Cornelissen G**, Mojto V, Fatima G, Wichansawakun S, Singh M, Kartikey K, Sharma JP, Torshin VI, Chibisov S, Kharlitskaya E, Al-baraweed OA. Effects of circadian restricted feeding on parameters of metabolic syndrome among healthy subjects. *Chronobiology Int.* in press. <https://doi.org/10.1080/07420528.2019.1701817>
 20. Gubin DG, **Cornelissen G**. Factors that must be considered while solving the problem of adequate control of blood pressure. *Journal of Chronomedicine* 2019; 1; in press.
 21. **Cornelissen G**, Otsuka K, Gubin D. Honoring Gennady Gubin and his lifetime achievements. *Journal of Chronomedicine* 2019; 1; in press.
 22. **Cornelissen G**, Watanabe Y, Beaty LA, Turner AC, Sothorn R, Siegelova J, Breus T, Gubin D, al-Abdulgader AA, McCraty R, Otsuka K. As-one-goes blood pressure and heart rate monitoring: a chronobiologic approach with applications in clinical practice and basic science. *Heart and Mind*, submitted (by invitation).
 23. Neroev V, Gubin D, Malishevskaya T, Astakhov YS, Astakhov SY, Kolomeichuk S, **Cornelissen G**, Bogdanova D, Weinert D. Disruption of intraocular pressure 24-hour rhythm correlates with retinal ganglion cell loss in glaucoma. *Ophthalmology*, Submitted for publication.
 24. Luszczek ER, Parsons L, Elder J, Harvey SB, Skube M, Muratore S, Beilman G, Cornelissen-Guillaume G. Metabolomics pilot study identifies circadian desynchronization and distinct inpatient variability patterns in critical illness. Submitted for publication.
 25. Saka F, **Cornelissen G**. Chronobiologic assessment of the effect of the DASH diet on blood pressure. In preparation.
 26. **Cornelissen G**, Bhatt ML, Singh RB. Memoriam: Professor BD Gupta. *World Heart J* 2018; 10 (4): 351-352.
 27. **Cornelissen G**, Halberg F. Remembering BD Gupta. *World Heart J* 2018; 10 (4): 353-356.
 28. Elkilany G, Hristova K, Singh RB, Pella Do, Pella Da, Fedacko J, Maheswari A, Verma NS, **Cornelissen G**. Memoriam: Dr. Hilton Chaves Jr, (Born March 18, 1955; Deceased August 28, 2018). *World Heart J* 2018; 10 (4): 357-363.
 29. **Cornelissen G**. In honor of Earl Bakken and Franz Halberg. *World Heart J* 2018; 10 (4): 365-371.
 30. **Cornelissen G**, Sackett Lundeen L. Remembering Hans Werner Wendt (25 July 1923 – 31 January 2019). *World Heart J* 2019; 11 (2): 179-183.